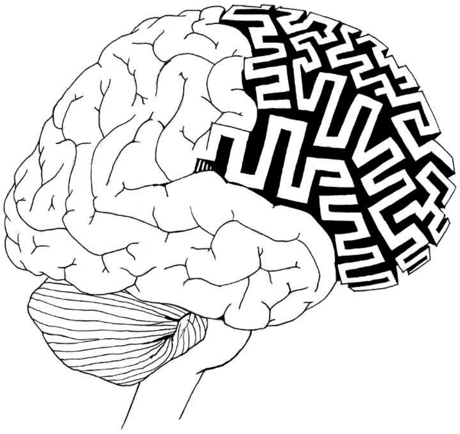
# AREADNE 2010

Research in Encoding and Decoding of Neural Ensembles
Nomikos Conference Centre, Santorini, Greece
17–20 June 2010



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**AREADNE 2010**
*Research in Encoding and Decoding of Neural Ensembles*
*Nomikos Conference Centre, Santorini, Greece, 17–20 June 2010*
N. G. Hatsopoulos and J. S. Pezaris, editors
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# WELCOME

## Welcome

Welcome to AREADNE 2010, the third AREADNE Conference on Research in Encoding and Decoding of Neural Ensembles.

One of the fundamental problems in neuroscience today is to understand how the activation of large populations of neurons gives rise to the higher order functions of the brain including learning, memory, cognition, perception, action and ultimately conscious awareness. Electrophysiological recordings in behaving animals over the past forty years have revealed considerable information about what the firing patterns of single neurons encode in isolation, but it remains largely a mystery how collections of neurons interact to perform these functions.

Recent technological advances have provided a glimpse into the global functioning of the brain. These technologies include functional magnetic resonance imaging, optical imaging methods including intrinsic, voltage-sensitive dye, and two-photon imaging, high-density electroencephalography and magnetoencephalography, and multi-microelectrode array electrophysiology. These tools and techniques have expanded our knowledge of brain functioning beyond the single neuron level.

At the same time, our understanding of how neuronal ensembles carry information has allowed the development of brain-machine interfaces (BMI) to enhance the capabilities of patients with sensory and motor deficits. Knowledge of how neuronal ensembles encode sensory stimuli has made it possible to develop perceptual BMIs for the hearing and visually impaired. Likewise, research in how neuronal ensembles decode motor intentions has resulted in motor BMIs by which people with severe motor disabilities can control external devices.

## Conference Mission Statement

There are three major goals of this conference. First and foremost, this conference is intended to bring scientific leaders from around the world to present their recent findings on the functioning of neuronal ensembles. Second, the meeting will provide an informal yet spectacular setting on Santorini in which attendees can discuss and share ideas outside of the presentations at the conference center. Third, this conference continues our long term project to form a systems neuroscience research institute within Greece to conduct state-of-the-art research, offer meetings and courses, and provide a center for visiting scientists from around the world to interact with Greek researchers and students.

## Organizing Committee

The AREADNE 2010 conference was organized by Nicholas Hatsopoulos (Co-Chair) and John Pezaris (Co-Chair), Andreas Tolias, Catherine Ojakangas, Thanos Siapas, and Yiota Poirazi.

## Local Organizers

Local organization effort has been provided by Nike Makris with assistance from Erika Berry and Josh Markey.

## Sponsors and Support

Our conference is being sponsored with a generous gift from Dr. and Mrs. George Hatsopoulos to The AREADNE Foundation, a non-profit organization newly incorporated to run the AREADNE Conferences. In addition, for 2010, the conference is being administered by the Massachusetts

General Hospital, with grant or in-kind support from the National Institute of Neurological Disorders and Stroke (Grant Number R13NS066636), part of the United States National Institutes of Health, the U.S. National Science Foundation (Grant Number 1005436), Foley & Lardner, LLC, The Burroughs Wellcome Fund (Award Number 1008916), and The Center for Integrative Neuroscience and Neuroengineering Research, a joint effort between the University of Chicago and the Illinois Institute of Technology. Any opinions, findings and conclusions or recommendations expressed in this document are the sole responsibility of the editors and contributors and do not necessarily reflect the official views of any of these individuals or institutions.

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CINNR Co-Director, University of Chicago
*Dr. Ulinski recently passed away; his name remains here in tribute.*

## The Myth of Ariadne

The conference name AREADNE is a combination of the conference title, Research in Encoding and Decoding of Neural Ensembles, and the name of the mythological figure Ariadne. Our brain-to-maze logo was inspired by the central role Ariadne played in the myth of Theseus and the Labyrinth.

Ariadne was the daughter of Minos, king of Crete. King Minos built a large, intricate maze called the Labyrinth to house the Minotaur, a fearsome creature that was half bull, half human. Any who attempted to face the Minotaur perished, either by becoming lost in the maze or from the Minotaur's vicious attack. When the hero Theseus came from Athens to slay the Minotaur, Ariadne gave him a sword and a ball of silk thread. Theseus tied one end of the thread at the Labyrinth entrance and unwound it as he went along, so that after he had found and slain the Minotaur, he could escape from the maze by following the thread back out.

# LOCAL INFORMATION

We have assembled a small selection of local information on Fira and the island of Thera. For additional information, we recommend selecting one of the many guidebooks that have been written on island travel in Greece.

### Restaurant Information

Greeks normally eat their evening meal quite late, with restaurants being busiest 10 PM to midnight. The largest meal of the day is often lunch, leading naturally to the habitual afternoon nap. Tipping at restaurants is not expected, as the cost of service is normally included in the price of the meal. Each euro symbol is about € 10.

*Restaurants in Fira*

| | | | |
|---|---|---|---|
| Ambelos | +30-22860-22544 | € € | caldera view, wine restaurant |
| Archipelagos | +30-22860-23673 | € € € | caldera view, Santorini cuisine |
| Koukoumavlos | +30-22860-22510 | € € € € | caldera view, nouvelle cuisine |
| Nikolas | +30-22860-24550 | € | Greek cuisine, next to Town Club |
| Poldo | +30-22860-24004 | € | souvlaki stand, near the National Bank |
| Saltsa | +30-22860-28018 | € € € | Greek nouvelle cuisine |
| Sphinx | +30-22860-23823 | € € € € | Greek cuisine, caldera view |
| The Greeks | +30-22860-22989 | € € | taverna, near the cable car |

*Restaurants in Oia*

| | | | |
|---|---|---|---|
| Iliovassilema | +30-22860-71614 | € € | fresh fish |
| Thalami | +30-22860-71009 | € € | ouzo bar |
| 1800 | +30-22860-71485 | € € € € | nouvelle cuisine |

*Restaurants in Perivolos-Vlychada*

| | | | |
|---|---|---|---|
| Vlychada | +30-22860-82819 | € € | Greek taverna by the beach |
| The Net | +30-22860-82818 | € € € € | fish tavern by the sea, local cuisine |

### Recommended Activities

Santorini offers not just sweeping vistas, but excellent nightlife, a respectable wine industry, beaches with white, black, or red sand, ancient excavations, and fantastic sunsets. Also, we have optional tours to the Ancient Thera archaeological site and to the volcano island at the center of the caldera, although these may not be able to accommodate everyone. Beyond these two excursions (which can be taken on your own, although without the benefit of our invited experts), there are plenty of other activities on the island. A few suggestions to scratch the surface are listed below.

*Archaeological Museum at Fira*
open 08.30–15.00 (closed Mondays), tel +30-22860-22217, Ypapantis Street, Fira

*Museum of Prehistoric Thera*
open 08.30–15.00 (closed Mondays), tel +30-22860-23217, Mitropoleos Street, Fira

*Folk Art Museum*
open 10.00–14.00 and 18.00–20.00, tel +30-22860-22792, Kondohori, near Fira

*Wine Museum*
open daily 12.00–20.00, tel +30-22860-31322, located in Vothonas village

*Oia at sunset*
sunset is at approximately 8 pm in late June; once at Oia, follow the crowds westward

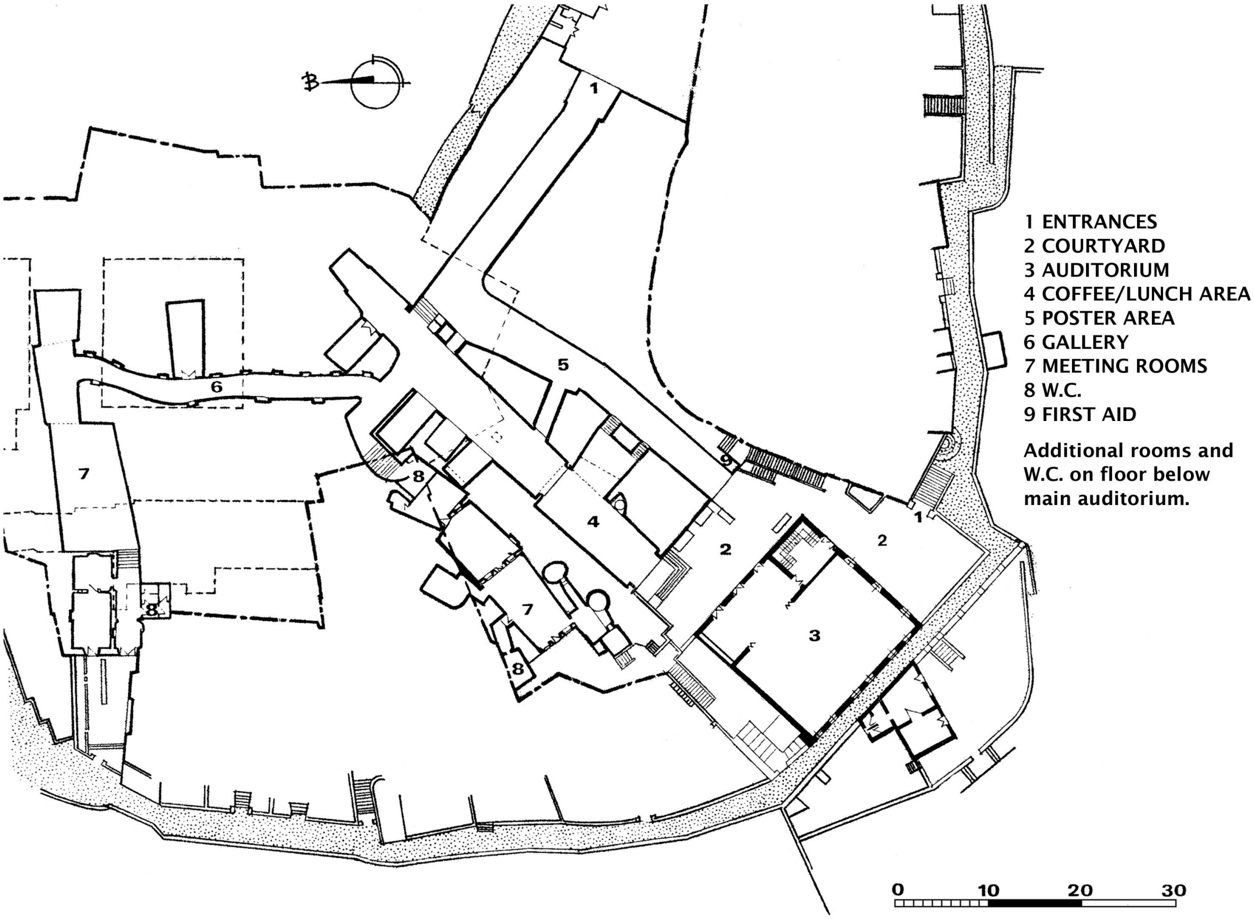
*Monastery of Profitis Ilias*
in Pyrgos, at the mountain peak; has a nice ecclesiastic museum

### Main Beaches

The beaches on Santorini are beautiful and varied, with white, red, and black sand depending on location. However, swimming must be done with some care as the water gets deep very quickly and rip currents are not uncommon. Flip-flops are a must as the dark sand can get extremely hot in the sun. SCUBA diving is available with trips to wrecks, the volcano, and the underwater caldera face. Beaches are at Perivolos (13 km from Fira), Perissa (13 km), Vlychada (12 km), and Kamari (10 km).

### Conference Centre Map

Oral presentations will be held in the main auditorium of the Centre. Coffee breaks will be held in the reception area and courtyard. Posters will be hung on the walls of the passage from the courtyard to the gallery. A first aid station will be available. Please refer to the map below for more details.



# DAILY SCHEDULE AND PROGRAM

## Overall Schedule

The schedule for the four-day conference follows the Greek lifestyle of having a long lunch, with the afternoon free for siestas or swimming, and a late dinner.

*Wednesday*

| | |
|---|---|
| 19:00–21:00 | welcome reception |

*Thursday*

| | |
|---|---|
| 08:00–08:30 | registration |
| 08:30–09:00 | opening remarks |
| 09:00–12:30 | lectures and coffee break |
| 12:30–14:00 | lunch |
| 17:00–21:30 | lectures and coffee break, posters |

*Friday*

| | |
|---|---|
| 09:00–12:30 | lectures and coffee break |
| 12:30–14:00 | lunch |
| 17:00–21:30 | lectures and coffee break, posters |

*Saturday*

| | |
|---|---|
| 09:00–12:00 | optional excursions (no lunch provided) |
| 17:00–21:30 | lectures and coffee break, posters |

*Sunday*

| | |
|---|---|
| 09:00–12:30 | lectures and coffee break |
| 12:30–14:00 | lunch |
| 17:00–19:00 | lectures and coffee break |
| 19:00–19:30 | closing remarks |
| 21:00–24:00 | banquet dinner at Vanilia Restaurant |

## WEDNESDAY, 16 JUNE 2010

19:00–21:00 welcome reception at Nomikos Centre

## THURSDAY, 17 JUNE 2010

08:00–08:30 registration

08:30–09:00 opening remarks

### MORNING SESSION John Pezaris, moderator

09:00–09:45 **Carlos Brody** (Princeton University) *Neocortical contributions to orienting decisions in the rat*, 21

09:45–10:30 **Bijan Pesaran** (New York University) *Neural activity in area LIP and PRR during coordinated decisions and actions*, 37

10:30–11:00 coffee break

11:00–11:45 **David Freedman** (University of Chicago) *The parietal cortex: space . . . and beyond*, 29

11:45–12:30 **Georgia Gregoriou** (University of Crete) *Dynamics of interactions between prefrontal and visual cortex in attention*, 30

12:30–14:00 lunch

### AFTERNOON SESSION Tony Movshon, moderator

17:00–17:45 **Matteo Carandini** (University College London) *Regimes of computation in visual cortex*, 22

17:45–18:15 coffee and light snacks

18:15–19:00 **Irini Skaliora** (Institute for Biomedical Research of the Academy of Athens) *Crossmodal developmental plasticity: learning to match sound and vision*, 44

19:00–19:45 **Robert Desimone** (Massachusetts Institute of Technology) *Neural synchrony and selective attention*, 24

20:00–21:30 posters, presenting author

**Nikolaos Aggelopoulos** (MPI Biological Cybernetics) *Cholinergic dependence of a cognitive task*, 46

**Robbe Goris** (University of Leuven) *Neural population code model for pattern detection*, 63

**Kate Gross** (McGill University) *Real-time sub-second measurement of oxygen fluctuation can increase the information extracted from the brain for use in neural prosthetic systems*, 64

**Linda Hermer** (University of Florida) *Interactions between primary motor cortex and secondary olfactory cortex during an olfactory-guided decision making task*, 65

## FRIDAY, 18 JUNE 2010

**MORNING SESSION** Gilles Laurent, moderator

09:00–09:45 **Wolf Singer** (Max Planck Institute for Brain Research) *Distributed processing and temporal codes in cortical networks*, 43

09:45–10:30 **Helen Barbas** (Boston University) *Cortical communication rules*, 20

10:30–11:00 coffee break

11:00–11:45 **Shy Shoham** (Technion) *Advances in the physical control and analysis of correlated neural population activity*, 41

11:45–12:30 **Jeff Lichtman** (Harvard University) *Connectomics in the developing nervous system*, 33

12:30–14:00 lunch

**AFTERNOON SESSION** Nicholas Hatsopoulos, moderator

17:00–17:45 **Michael Shadlen** (HHMI and University of Washington) *Variance, expectations, correlation and islands*, 40

17:45–18:15 coffee and light snacks

18:15–19:00 **Maneesh Sahani** (University College London) *Keeping one’s eye on the ball: inferring latent dynamical state from ensemble neuronal activity*, 39

19:00–19:20 **Nike Makres** (Hellenic Education and Research Center) *Greek city states and Western civilization*, 35

19:20–19:40 **Desmond Patterson** (Australian National University) *The Minoan eruption of 1610 BC: magnitude and mechanism*, 36

20:00–21:30 posters, presenting author

**Christoph Kayser** (MPI Biological Cybernetics) *The time scales of information representation in auditory cortex are stimulus dependent*, 66

**Bjørg Elisabeth Kilavik** (INCM / CNRS) *Motor cortical evoked local field potentials are sensitive to visuomotor task timing and performance, and are modified by longterm daily practice*, 67

**Lynne Kiorpes** (New York University) *Analysis of funtional circuitry in primary visual cortex of amblyopic monkeys*, 68

**Andreas Koupparis** (University of Patras) *A high-theta rhythm in the fronto-posterior direction appears during the K-complex in NREM stage II of human sleep*, 69

**Xanthippi Konstantoudaki** (IMBB/FORTH) *Distinct interneuron types shape persistent activity properties in a PFC microcircuit model*, 70

**Achilleas Koutsou** (University of Cyprus) *Causes of firing in cortical neurons revisited: temporal integration versus coincidence detection*, 71

**Philipp Lies** (MPI Biological Cybernetics) *What is the goal of complex cell coding in V1?*, 72

**Kyle Lillis** (Mass. General Hospital) *An excitatory role for gabaergic interneurons in 4-ap-induced ictal events*, 73

**Wasim Malik** (Harvard Medical School) *Low-complexity decoding in intracortical neural interfaces for humans with tetraplegia*, 74

**Khaled Masmoudi** (CNRS/UNSA and INRIA) *Encoding and decoding stimuli using a biologically realistic model: the non-determinism in spike timings seen as a dither signal*, 75

**Alexander Mathis** (BCCN Munich) *How good is grid coding versus place coding for navigation using noisy, spiking neurons?*, 76

**Alberto Mazzoni** (Italian Inst. of Technology) *Primary visual cortex (V1) encodes complementary information about naturalistic movies at different temporal scales*, 77

**David Melcher** (University of Trento) *Decoding object categories from EEG signals on single trials*, 78

**Rumyana Kristeva** (Univ. Freiburg) *Synchronization between motor cortex and muscle: high-resolution EEG studies*, 79

**Tomislav Milekovic** (BCCN Freiburg) *An online brain-machine interface using decoding of movement direction from the human electrocorticogram*, 80

**Giuseppe Notaro** (Dist University of Genova) *Temporal patterns of neural activity in rat somatosensory cortex correlate with trial-to-trial perceptual judgements in a two texture discrimination task*, 81

**Fanis Panagiotaropoulos** (MPI Biological Cybernetics) *Reduction of correlated noise in the macaque prefrontal cortex during conscious visual perception*, 82

**Athanasia Papoutsi** (IMBB/FORTH) *Microcircuits in the prefrontal cortex: in silico investigation of their role in the emergence, maintenance and termination of persistent activity*, 83

**Dionysios Perdikis** (Univ. of the Mediterranean) *Functional architectures: coding for structured flows on manifolds embedded in a hierarchy of time scales*, 84

**Laurent Perrinet** (DyVA - INCM / CNRS) *Dynamical emergence of a neural solution for motion integration*, 85

## SATURDAY, 19 JUNE 2010

09:00–13:00 optional excursions (no lunch provided)

**AFTERNOON SESSION** Erin Schuman, moderator

17:00–17:45 **Michael Häusser** (University College London) *Dendritic computation*, 32

17:45–18:15 coffee and light snacks

18:15–19:00 **Alcino Silva** (University of California, Los Angeles) *Molecular and cellular mechanisms of memory allocation in neuronal networks*, 42

19:00–19:45 **Melina Hale** (University of Chicago) *Functional organization of simple neural circuits in zebrafish motor systems*, 31

20:00–21:30 posters, presenting author

**Peter Petersen** (University of Copenhagen) *Neuronal population coding in vertebrate cpg: a multi-unit study during functional motor activity*, 86

**Adrián Ponce-Alvarez** (CNRS-INCM) *Statistics of cortical up and down states during sleep*, 87

**Alexandro Ramirez** (Columbia University) *Decoding birdsong from auditory midbrain neurons*, 88

**Sylvia Schröder** (Inst. of Neuroinformatics) *Heterogeneity in the responses of neighboring neurons in cat primary visual cortex*, 89

**Marianna Semprini** (Dist University of Genova) *A parametric study of information transfer between stimulating and recording electrodes in a closed loop brain machine interface*, 90

**Maryam Shanechi** (MIT) *A real-time brain-machine interface combining plan and peri-movement activities*, 91

**Oren Shriki** (Ben-Gurion University) *Spike latency coding of orientation in the primary visual cortex*, 92

**Rodrigo Sigala** (MPI Biological Cybernetics) *Categorical representation of a human/monkey face continum in the human and non-human primate temporal lobe*, 93

**Richard Stacey** (McGill University) *A graph theory approach to neuronal ensemble decodes*, 94

**Aaron Suminski** (University of Chicago) *Multisensory feedback improves the performance of a corticallycontrolled brain-machine interface*, 95

**Francois Szymanski** (Istituto Ital. di Tecnologia) *Laminar and temporal distribution of stimulus information in local field potentials*, 96

**Ariel Tankus** (Technion) *Decoding movement direction from the activity of multiple neurons in the human frontal lobe*, 97

**Jiannis Taxidis** (University of Nottingham) *Effects of CA3 bursts on CA1 activity examined through a simple CA3CA1 spiking network*, 98

**Aldemar Torres Valderrama** (Univ. Med. Center Utrecht) *The bereitschafts cross-potential: synchronizing neuronal assemblies in volitional movement*, 99

**Mikkel Vestergaard** (University of Copenhagen) *Population activity in a spinal motor network monitored with extracellular multi-electrode recordings during multiple functions and during local drug delivery*, 100

**Michael Vidne** (Columbia University) *A common-input model of a complete network of ganglion cells in the primate retina*, 101

**Ioannis Vlachos** (BCCN Freiburg) *How do distinct neuronal subpopulations in the central amygdala shape the fear response? – a computational model*, 102

**Stavros Zanos** (Univ. of Washington) *Performance of subdural electrocoticography arrays to record and stimulate the sensorimotor cortex of nonhuman primates*, 103

**Theodoros Zanos** (McGill University) *Spectral contamination and efficient removal of spike remnants from local field potentials*, 104

## SUNDAY, 20 JUNE 2010

**MORNING SESSION** Eilon Vaadia, moderator

09:00–09:45 **Eberhard Fetz** (University of Washington) *Learning and plasticity in neural populations with recurrent brain-computer interfaces*, 27

09:45–10:30 **Jose Carmena** (University of California, Berkeley) *Neural adaptations to a brain-machine interface*, 23

10:30–11:00 coffee break

11:00–11:45 **Adrienne Fairhall** (Univ. of Washington) *Optimality in neural adaptation*, 26

11:45–12:30 **Tamar Flash** (Weizmann Institutes of Science) *Motion generation and perception: geometry, timing and compositionality*, 28

12:30–14:00 lunch

**AFTERNOON SESSION** Kenny Blum, moderator

17:00–17:45 **Nikos Logothetis** (Max Planck Institute for Biological Cybernetics) *Electrical microstimulation and fMRI*, 34

17:45–18:15 coffee and light snacks

18:15–19:00 **Barry Richmond** (National Institute of Mental Health) *Molecular tools: uses and promise for studying brain circuits underlying higher function*, 38

19:00–19:45 **Timothy Ebner** (University of Minnesota) *Flavoprotein optical imaging of cerebellar circuits*, 25

19:45–20:00 closing remarks

21:00–24:00 banquet dinner at Vanilia Restaurant

# SPEAKER ABSTRACTS
## (in alphabetical order by speaker)

## CORTICAL COMMUNICATION RULES

*Helen Barbas*

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Most synapses in the cortex occur between neurons within a cortical column. Short and long distance connections that interlink different cortices, or the cortex with the thalamus or other subcortical structures, account for a comparatively small proportion of cortical synapses, but have varied and profound effects on the activity of cortical columns. Specific influences of cortical pathways depend on their layer of origin and termination, size of presynaptic terminal, and synaptic interactions with excitatory neurons, or distinct classes of inhibitory neurons that vary in efficacy of inhibitory control. The prefrontal cortex has widespread connections with excitatory and inhibitory systems in the cortex, the thalamus, amygdala, and other structures. Using the prefrontal cortex as a model system we have provided evidence that the laminar distribution of corticocortical connections varies predictably by the architectonic (structural) relationship of the linked areas. This structural model for connections has provided the framework to study and provide evidence of remarkable specificity in the synaptic connections of prefrontal areas with laminar-specific and functionally distinct neurochemical classes of inhibitory neurons in the cortex, and specialized inhibitory systems in the thalamus and the amygdala. These interactions may underlie shifts in neural rhythms that determine the state of consciousness, ranging from a quiet state to active attention needed for cognitive operations, or emotional vigilance.

Support

NIH grants from NINDS and NIMH, and an NSF CELEST grant

# NEOCORTICAL CONTRIBUTIONS TO ORIENTING DECISIONS IN THE RAT

*Carlos D. Brody*[*], *Bingni W. Brunton, Jeffrey C. Erlich, Max Bialek*

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Behaviors that require deciding between orienting to one direction versus orienting to another have long been investigated in rodents. Nevertheless, the rodent neocortical contribution to these decisions has been surprisingly little studied. One area of potential interest is the Frontal Orienting Field, a large bilateral area in the frontal cortex of the rat brain that is estimated to be 4 $\mathrm{mm}^2$ in size on each side. Anatomical, microstimulation, and lesion studies have suggested that the FOF may be homologous to primate frontal premotor areas such as the Frontal Eye Field (FEF) or Supplementary Motor Area (SMA). Surprisingly, we have been able to find only two electrophysiological studies performed so far in rodent FOF. Here I will present behavioral, pharmacological inactivation, and extracellular recording data from the FOF in rats performing a simple delayed orienting task. These data demonstrate that the rat FOF is involved in motor planning and/or preparation.

To further study orienting decisions in the rat, we have developed a task that requires temporal integration of evidence. During each trial of this task, subjects hear a series of randomly timed clicks from two well-separated speakers. The subjects must report which speaker played the greater total number of clicks. This requires keeping a running counter of clicks (*i.e.*, integrating clicks) over the stimulus period. We call the task the *Poisson clicks* task. Here I will describe the task and its advantages, and I will show that behavior of rats trained to perform this task is well-fit by a slightly leaky, noisy, integrator model in which the time constant of integration is approximately 1 second or longer. Such a long integration timescale establishes both the Poisson clicks task and rats as appropriate substrates for studying neural integration in decision-making.

# REGIMES OF COMPUTATION IN VISUAL CORTEX

*Matteo Carandini*

Institute of Ophthalmology, University College London, London, UK
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The perception of visual stimuli is widely held to be supported through the activity of populations of neurons in visual cortex. Work in our laboratory seeks to record this population activity through optical and electrical imaging and to characterize its evolution in time. The results indicate that the visual cortex operates in a regime that depends on the strength of the visual stimulus. For large, high contrast stimuli, the cortex operates in a manner that emphasizes local computations, whereas for smaller or lower contrast stimuli the effect of lateral connections becomes predominant. In this interconnected regime, the population responses exhibit rich dynamics, with waves of activity that travel over 2–6 millimeters of cortex to influence distal locations. These waves are strongest in subthreshold activity but are also present in spike responses. In the complete absence of a stimulus, these waves dominate, and are sufficient to explain the apparently erratic activity of local populations. These results indicate that two apparently contradictory views of visual cortex, one postulating computations that are entirely local and the other postulating strong lateral connectivity, are both correct. The cortex can operate in both regimes, and makes its choice of regime adaptively, based on the stimulus conditions. Not all neurons, however, participate to the same extent in these network phenomena: recent evidence indicates that the behavior of simple and complex cells is quite different, with simple cells being mostly correlated with the stimulus, and complex cells being strongly correlated with the activity of the rest of the population.

# NEURAL ADAPTATIONS TO A BRAIN-MACHINE INTERFACE

*Jose Carmena*

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Research in Brain-Machine Interfaces (BMIs) has led to demonstrations of rodents, non-human primates and humans controlling prosthetic devices in real-time through modulation of neural signals. In particular, cortical BMI studies have shown that improvements in performance require learning and are associated with a change in the directional tuning properties of units directly incorporated into the BMI (*direct units*). However, little is known about modifications to neurons in the surrounding cortical network (*indirect units*) during neuroprosthetic control. Moreover, the time course and the reversibility of any such changes remain unclear. Using stable recording from large ensembles of units from primary motor cortex in two macaque monkeys, here we demonstrate that proficient neuroprosthetic control reversibly reshapes cortical networks through local effects. By monitoring large ensembles of both direct and indirect units during long-term neuroprosthetic control, we observed large-scale changes in the preferred direction and the depth of modulation of indirect units. Strikingly, proficient control was specifically associated with an apparent distance-dependent reduction in modulation depth. These observed changes were also rapidly reversible in a state-dependent manner. Thus, ensemble control of a neuroprosthetic device appears to triggers large-scale modification of cortical networks centered on units directly incorporated in the BMI.

# NEURAL SYNCHRONY AND SELECTIVE ATTENTION

*Robert Desimone*

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Neurophysiological studies in monkeys have identified some of the neural mechanisms of attentional selection within the ventral, *object recognition*, stream of the cortex, which begins with area V1 and continues through areas V2, V4, and IT cortex. At each stage along this stream, attended, or behaviorally relevant, stimuli are processed preferentially compared to irrelevant distracters. Although these enhancing effects of attention have been well-established, the effects of attention on object recognition performance in cluttered scenes has never actually been measured at the population level. We have therefore used neural population decoding to analyze how spatial attention influences object classification by neurons in inferior temporal (IT) cortex of macaques performing a spatial attention task. Without attention, object classification performance for an array of three complex objects was close to chance. However, with attention to one object, classification performance was similar to that when the attended object was presented in isolation. Thus, by the final stage of visual processing in the ventral visual stream, attentional mechanisms have resulted in an almost complete elimination of clutter.

Given that the phenomenology of attentional effects on visual responses has been largely established, we have recently focused on the detailed mechanisms by which the attentional feedback affects cells in visual cortex. Our work has suggested that the attentional bias is mediated, at least in part, in visual cortex through an increase in high-frequency (gamma) synchronization of neurons carrying critical information about the location or features of the behaviorally relevant stimulus. Increases in gamma synchrony are found during both spatial attention and featural attention engaged during visual, and the presence of synchrony in visual cortex predicts faster responses in visual tasks.

Recent evidence shows that inputs from the frontal eye fields (FEF) in prefrontal cortex initiate coupled gamma-frequency oscillations between FEF and area V4 in the ventral stream during attention, and these oscillations are phase, or time-shifted to allow for conduction and synaptic delays between the two areas, thereby achieving maximally effective communication. Attentional effects in V2 and V1, which are earlier stages in the ventral stream, occur later than in V4, suggesting that attentional feedback works backwards, step by step through the ventral stream. Our recent human experiments using magnetoencephalograpy (MEG) show results that are remarkably similar to those found in animals.

Finally, although most studies of attention in visual cortex have focused on spatially directed attention, we also know that attention to visual features modulates visual processing to a similar degree. Our recent recordings in FEF and area V4 reveal possible mechanisms for top-down attention to visual features in both areas.

# FLAVOPROTEIN OPTICAL IMAGING OF CEREBELLAR CIRCUITS

*Timothy J. Ebner*

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Understanding the spatial and temporal patterns of activity are key to deciphering the information processing occurring in central nervous system circuits. The cerebellar cortex, with its stereotypic circuitry and transverse and parasagittal architectures, is an ideal structure to use activity-dependent optical imaging. This talk describes using flavoprotein autofluorescence optical imaging in the cerebellar cortex, *in vivo*, to study the organization of the cerebellar cortical circuitry and synaptic plasticity as well as dysfunction of these processes in cerebellar diseases. The flavoprotein signal is mitochondrial in origin and is due to the oxidation and reduction of flavoproteins in relation to oxidative metabolism. Closely coupled to neuronal activity, the flavoprotein signal can be used to monitor both excitation and inhibition. Parallel fibers, a central element in most theories of cerebellar function, have been assumed to result in uniform activation of their post-synaptic targets along a folium. Flavoprotein imaging has uncovered a spatial organization by which the transversely oriented parallel fibers differentially activate Purkinje cells and molecular layer neurons in parasagittal zones. In addition to the activation of a beam of Purkinje cells at short latency, low frequency parallel fiber stimulation also activates molecular layer interneurons that generate parasagittal bands of inhibition. At a much longer latency, high frequency parallel fiber stimulation evokes patches of increased activity organized in parasagittal bands. Parallel fiber stimulation also generates a long-term potentiation (LTP) of both the short latency beam response and the long latency patch responses. Both the parasagittal zonation and LTP are due to the activation of type 1 metabotropic glutamate receptors (mGluR1). Therefore, parallel fibers engage Purkinje cells and molecular neurons in parasagittal zones through an mGluR1 channel. Flavoprotein imaging is also revealing new insights into dysfunction of these circuits in cerebellar diseases. For example, in a mouse model of spinocerebellar ataxia type 5, there is a abnormal distribution of mGluR1 receptors on Purkinje cells and marked loss of the LTP of the beam and the patches. In a mouse model of episodic ataxia type 2, imaging uncovered intrinsic low frequency oscillations in the cerebellar cortex that can account for the characteristic episodic movement disorder in this P/Q calcium channelopathy. With many new developments in optical imaging at hand, this technique will prove increasing important in investigating the spatial and temporal patterns of activity in the nervous system.

# OPTIMALITY IN NEURAL ADAPTATION

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Nervous systems tune themselves to the statistical structure of the stimuli they encounter. This sensitivity to statistics appears in phenomena ranging over many timescales, from the adaptation of vision to a rapid change in light level to the loss of ability to distinguish the sounds of non-native languages. While multiple neural mechanisms contribute to this on-line learning of stimulus distributions, we show that the intrinsic nonlinearities of single neurons provide them with the ability to represent time-varying stimuli optimally. While such sensitivity to stimulus statistics does not require learning, slower timescales of adaptation are consistent with optimal inference of statistical parameters of the changing stimulus ensemble. Finally, we discuss the consequences of rapid single-neuron gain control for transmission of information in a network.

# LEARNING AND PLASTICITY IN NEURAL POPULATIONS WITH RECURRENT BRAIN-COMPUTER INTERFACES

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The neural networks of the brain are organized to adapt to consistent sensorimotor contingencies. We are investigating the brain's adaptation to artificial connections produced by an autonomous recurrent brain-computer interface [R-BCI] that operates continuously during free behavior and generates activity-dependent stimulation of the brain or muscles. This *Neurochip* consists of battery-powered electronics connected to electrodes that record the activity of motor cortex cells and/or muscles. The neural activity is processed by programmable computer chips and can be converted in real-time to activity-contingent electrical stimuli delivered to nervous system sites or muscles (1). A promising application is to bridge impaired biological connections, as demonstrated for cortically controlled electrical stimulation of paralyzed forearm muscles. A recent study (2) demonstrated that learning volitional control of the relevant neural activity is a promising alternative to the traditional decoding of neural populations for BCI control. A second application of the R-BCI is to produce Hebbian synaptic plasticity through spike-triggered stimulation, which can strengthen physiological connections (3). The R-BCI paradigm has numerous potential applications, depending on the input signals, the computed transform and the output targets. We are currently exploring several new applications, including EMG-triggered cortical stimulation and cortically controlled intraspinal stimulation.

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# MOTION GENERATION AND PERCEPTION: GEOMETRY, TIMING AND COMPOSITIONALITY

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Behavioral and theoretical studies have focused on identifying the kinematic and temporal characteristics of various movements ranging from simple reaching to complex drawing and curved motions. These kinematic and temporal features were quite instrumental in investigating the organizing principles that underlie trajectory formation and the problem of motor compositionality. Similar kinematic constraints play also a critical role in visual perception of abstract and biological motion stimuli and in action recognition. In my talk I will describe the main findings from several brain mapping, psychophysical and neurophysiological studies aiming at identifying the neural correlates of the behavioral findings and to investigate the nature of neuronal representations (Dayan, *et al.*, 2007; Polyakov, *et al.*, 2009). I will also present a new theory of trajectory formation which is inspired by geometrical invariance (Bennequin, *et al.*, 2009). The theory proposes that movement duration, kinematics, and compositionality arise from cooperation among several geometries. Different geometries possess different measures of distance. Hence, depending on the selected geometry, movement duration is proportional to the corresponding distance parameter. Expressing these ideas mathematically, the theory led to concrete predictions concerning the kinematic and temporal features of both drawing and locomotion trajectories. In view of the theory's success in accounting for empirical observations, I will also discuss several of its implications concerning brain representations of motion, time and speed and the use of different mixtures of Euclidian and Non-Euclidian geometries in such representations.

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# THE PARIETAL CORTEX: SPACE . . . AND BEYOND

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A great deal of work has established that the parietal cortex plays an important role in spatial processing, including functions such as directing spatial attention and spatially-guided actions. However, recent work from a number of groups suggests that neuronal activity in parietal cortex is also likely involved in a number of non-spatial functions, including visual short-term memory, associative learning, and recognition of learned visual categories.

This talk will review a series of experiments aimed at understanding the respective roles of several interconnected cortical areas in and around the parietal cortex in encoding non-spatial visual factors, such as maintaining information in working memory and encoding visual categories. In addition, new data will be discussed which examines the relative roles of the posterior parietal and lateral prefrontal cortices, and suggests that the two areas likely play distinct roles in solving a visual categorization and decision-making.

# DYNAMICS OF INTERACTIONS BETWEEN PREFRONTAL AND VISUAL CORTEX IN ATTENTION

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Visual attention facilitates the selection and processing of stimuli that are relevant to behavior. When attention is guided by behavioral goals, rather than being captured automatically by the stimulus features, it is considered to be guided by top-down signals. It has been suggested that areas in the prefrontal (PFC) and posterior parietal (PPC) cortices provide top-down inputs to the visual cortex and this results in the selective enhancement of the representation of the behaviorally relevant stimulus.

To test whether the PFC can provide attention-related signals to the visual cortex and modulate activity of individual neurons in visual areas we conducted simultaneous recordings in the frontal eye field (FEF), an area within the PFC, and visual area V4. FEF neurons showed earlier firing rate changes due to attention than neurons in area V4 and could thus mediate attentional selection. Moreover, attention increased neuronal synchronization between the two areas in the gamma frequency range with phase relationships that can facilitate neuronal communication and increase the impact of the top-down inputs to the visual cortex. Our results indicated that inputs from FEF to V4 were dominant at the onset of attention to a location possibly mediating attentional selection, whereas inputs from V4 to FEF predominated during sustained attention. These results provide direct evidence on the role of FEF in attentional selection and begin to reveal how the dynamics of neuronal interactions between distant brain areas can allow the effective communication of distinct neuronal populations.

# FUNCTIONAL ORGANIZATION OF SIMPLE NEURAL CIRCUITS IN ZEBRAFISH MOTOR SYSTEMS

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In recent years, the zebrafish has emerged as a genetic model system that is advantageous for investigations of neural control of movement. Genetic and molecular approaches make manipulations in the system possible. Transparency of the organism in its larval stage facilitates physiological imaging and electrophysiology of identified neurons. We examine how populations of neurons in the brainstem and the spinal cord of the zebrafish control and coordinate startle behavior. The startle circuit is an accessible neural system for studying motor control since it involves relatively few, large cells and its activity results in a simple behavior. The location of the startle stimulus is reflected in the pattern and strength of activity of descending reticulospinal cells and spinal interneurons. The patterns of activity recorded determine the extent of axial bending and rotation around the center of mass during the response. By manipulating the organization and output of the reticulospinal startle neurons we are able to dissect the functions of components of the neural circuit. That work suggests that safety factors built into the startle circuit prevents aberrant neural activity from resulting in an inappropriate behavioral response.

# DENDRITIC COMPUTATION

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The computational power of dendrites has long been predicted using modeling approaches, but actual experimental examples of how dendrites solve computational problems are rare. I will present new results from experiments combining patch-clamp recordings with two photon imaging and glutamate uncaging demonstrating that cortical pyramidal neurons can discriminate spatiotemporal sequences of synaptic inputs along single dendrites. This provides a dendritic mechanism for pyramidal neurons to compute direction and velocity, and shows how dendrites can be used to decode spatiotemporal patterns of input.

# CONNECTOMICS IN THE DEVELOPING NERVOUS SYSTEM

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Connectional maps of the brain may have value in developing models of both how the brain works and how it fails when subsets of neurons or synapses are missing or misconnected. Such maps might also provide detailed information about how brain circuits develop and age. I am eager to obtain such maps in neonatal animals because of a longstanding interest in the ways neuromuscular circuitry is modified during early postnatal life as axonal input to muscle fibers is pruned. This *synapse elimination* may be part of the process whereby the nervous system molds itself to a particular epigenetic landscape. We have developed techniques to observe all the synaptic interactions at different sites in a developing muscle by generating transgenic mice in which the membranes of different axons are labeled different colors. These second generation Brainbow mice have allowed us to analyze the entire connectional maps of developing muscles. These connectomes show striking ordered patterns of connectivity that may be the origin of the ordered recruitment of muscle tension (*i.e.*, “size principle”). In brain however the density of neuropil is overwhelming, which has required development of lossless automated high resolution imaging of thousands of ultra thin (less than 30 nm) sections that are very large (about 4 mm$^2$). This approach aims at making large scale serial microscopic analysis of brain volumes routine.

# ELECTRICAL MICROSTIMULATION AND fMRI

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Electrical stimulation (ES) of the brain has been performed for over 100 years, and although some might say it is a crude technique for understanding the detailed mechanisms underlying different neural computations, microstimulation has made significant contributions to our knowledge in both basic and clinical research. Recently there has been resurgence in its use in the context of electrotherapy and neural prostheses. For example, ES has made it possible to at least partially restore hearing to deaf patients by delivering pulses via implanted electrodes to different regions of the cochlea. Stimulation of the basal ganglia is remarkably effective in restoring motor function to Parkinson's patients, and microstimulation of the geniculostriate visual pathway is regarded by some as a very promising (future) method for making the blind see again.

Yet, the methodology still suffers from at least two fundamental problems; (a) we do not always know exactly what is being stimulated when we pass currents through the tissue; and (b) stimulation causes activation in a large number of areas even outside the stimulation site, making it difficult to isolate and evaluate the behavioral effects of the stimulated area itself. Microstimulation during fMRI (esfMRI) could provide a unique opportunity to visualize the networks underlying electrostimulation-induced behaviors, to map neuromodulatory systems, or to develop electrotherapy and neural prosthetic devices. Moreover esfMRI is an excellent tool for the study of the effects of regional synaptic plasticity, *e.g.* LTP in hippocampus, on cortical connectivity. Last but not least, esfMRI can offer important insights into the functional neurovascular coupling. In my talk, I shall discuss findings from recent and on-going work on signal propagation during electrical stimulation, as well as data related to effective connectivity.

# GREEK CITY STATES AND WESTERN CIVILIZATION

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The Greek City States emerged ca. 800 B.C. when the world only knew vast theocratic empires ruled by autocratic kings. The Greek city states were a curiosity: small in size, self governed, emphasizing the importance of individual initiative and laws written down in alphabetical script. The Greek term for city state is *polis* from which the English words *politics*, *political*, etc. derive. It is in the Greek *polis* that fundamental elements of western civilization emerged such as scientific method, rational thinking, legal justice and democratic government.

# THE MINOAN ERUPTION OF 1610 BC: MAGNITUDE AND MECHANISM

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Beautiful and bewitching, Santorini simply enthralls — this beauty, however, is borne of a dark and violent past. In the last 400,000 years the island has been wracked by 12 massive volcanic eruptions. The most recent of these (the Minoan eruption ca. 1610 BC) was truly catastrophic, with the total volume of ejecta now estimated at about 100 km$^3$. This is about 5 to 10 times larger than Krakatau (Indonesia, 1883), and 100 times St. Helens (USA, 1980). Eruptions of this magnitude are aptly termed *super-colossal* by vulcanologists — they are also quite rare, with only 6 occurring worldwide in the last 10,000 years.

The Minoan eruption was fed from a shallow (2–4 km) rhyodacitic (70–72 wt % $SiO_2$) magma chamber with a relatively high volatile content (about 3 wt % $H_20$). The vent was located somewhere near the northeast edge of the present Kameni islands, in the basin of a pre-existing, shallow, flooded caldera. In all, the eruption probably lasted about 4 days and can be divided into 3 major phases:

The initial (Phase 1) eruption was entirely subaerial, indicating the vent was on a central island similar to the present day Kamenis. During this stage the eruption was characterized by a violent supersonic (550 m/s) jet of steam and tephra. This mixed turbulently with the atmosphere to form a massive *plinian* column ascending to about 37 km altitude.

In Phase 2, the eruptive mechanism changed completely. Fissures developed in the pre-Kameni island allowing sea water to interact with the magma. The resultant extreme phreatomagmatic explosions resulted in clouds of tephra and steam expanding radially out from the vent in explosive rings called *base surges* — similar to the base surges observed around atomic tests at Bikini Atoll. Traveling at up to 200 km/h, these ascended the caldera walls and swept out and over the outer slopes of the volcano.

Phase 3 was the climatic phase of the eruption, and represents the logical progression into more energetic regimes as the influx of seawater increased. Two processes are noteworthy: First, the erosional widening of the vent reworked fragments of the pre-Kameni islands into the surge deposits. Second, the ongoing emptying of the underlying shallow magma chamber led to caldera collapse, foundering of the caldera floor, and rotational collapse of sections of the caldera wall to separate the islands of Therasia and Aspronisi from Thera.

The Kameni islands in the center of the present day caldera are comprised of young (less than 2 ka) dacitic ($SiO_2$ 64–67 wt %) lavas geochemically distinct from the tephras of the 1610 BC Minoan eruption. As such they represent the vanguard of the next magma batch to replenish and continue the 700,000 year history of this magnificent volcano — these will be the subject of the field excursion.

# NEURAL ACTIVITY IN AREA LIP AND PRR DURING COORDINATED DECISIONS AND ACTIONS

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We move our eyes not only to see the world better but also to guide our movements in the world more accurately. Often we are unaware of how we use our eyes to help us see and move better because the way we coordinate our eye and arm movements is so dynamic and flexible. During coordination, different areas of the brain become active and must communicate with each other in order to guide our eye and arm movements. Flexible communication between different brain areas is fundamentally important to a wide range of cognitive processes but very little is known about how brain areas talk to each other to guide our behavior. This talk will present our work developing looking and reaching as a model for understanding inter-areal communication employing simultaneous spike-field recordings in two areas of the posterior parietal cortex, the lateral intraparietal area (LIP) and the parietal reach region (PRR) during a sensory-motor coordination task and a decision coordination task.

# MOLECULAR TOOLS: USES AND PROMISE FOR STUDYING BRAIN CIRCUITS UNDERLYING HIGHER FUNCTIONS

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One might define neuroscience as the science that studies how mental activity arises from the organization and functionality of the underlying tissue. We would like to know how higher functions, such as perception, learning, memory, organization of behavior, arise from the interaction of neurons, no one of which is actually capable of any of these higher properties. The field has worked to understand this using behavioral analysis with lesions, physiology and pharmacology, that is, we perturb the system. The understanding coming from molecular biology provides the opportunity to control equivalent perturbations to the ones that have worked so well in the past with a higher level of precisions and control than has been possible before. These new tools make it imaginable to introduce perturbations at specific times and locations. Neurons or mechanisms can be specifically targeted with respect of their expression of a molecular marker (subtype), connection pattern, and/or location. In the full spectrum these tools offer the possibility of interfering with the function of a mechanism, or even adding a function. We have been pursuing several methods that offer opportunity to manipulate circuits and mechanisms. I will outline the ones that are under active study, and provide a progress report, including successes and set-backs, for the tools we are pursuing, and why we have chosen them. I will compare them to what we know about other approaches, and promise and drawbacks that are apparent, and what might be done to ameliorate the drawbacks.

# KEEPING ONE'S EYE ON THE BALL: INFERRING LATENT DYNAMICAL STATE FROM ENSEMBLE NEURONAL ACTIVITY

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Individual neurons in the mammalian neocortex do not act alone. Instead, they are embedded within densely interconnected columnar networks, and it is the collective dynamics of these networks which forms the substrate for the rich computational repertoire of the forebrain. Empirical access to these dynamics has historically been challenging, relying on inference either from isolated recordings of individual neurons or from aggregate measures such as local field potentials. Fortunately, the advent of large-scale multiple-neuron recording methods opens the possibility of characterising dynamics directly at the network scale.

I will discuss a family of analytic tools which may be used to recover dynamical *latent variables* (or *order parameters*) that capture the evolution of neural activity under controlled experimental conditions. These methods have been applied to recordings of neural activity in the motor and pre-motor cortices associated with movement preparation and execution. I will show how the methods facilitate visualisation of network activity on individual trials, and point to evidence that behaviourally relevant aspects of the network activity evolve smoothly and with a form of inertia.

# VARIANCE, EXPECTATIONS, CORRELATION AND ISLANDS

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I plan to discuss two ideas that bear on the fidelity of information represented by populations of neurons. The first is a fresh look at response variance measured in single neurons. We introduce a new measure of variance, based on the theory of doubly stochastic point process and the laws of total variance and covariance. Using neural recordings from area LIP, we show that this measure exposes computations that would be otherwise transparent to measures of firing rate. The second idea concerns the problem of noise correlations in populations of neurons. Whereas many data sets support weak noise correlation between pairs of neurons, a recent study (Ecker, *et al.*, 2010) demonstrates negligible pairwise noise correlation, on average, in visual cortex. The former observation suggests that the signal to noise ratio from averaging large ensembles of neurons is bounded, whereas the latter leaves open the possibility of unbounded improvement with larger neural populations. We will show that for the types of populations of neurons that one would consider as a candidate for averaging, the average pairwise correlation cannot be negative. Put another way, a large correlation matrix with enough negative pairwise correlations to balance out the positive correlations cannot be representative of an ensemble of random variables that one would average, add, subtract, and so forth. A homogeneous group of neurons that carry a common signal may have net positive pairwise correlation, but not a net negative correlation. Net negative correlation may be a signature of "islands" of neurons that modulate out of phase with each other and are thus poor candidates for averaging.

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## ADVANCES IN THE PHYSICAL CONTROL AND ANALYSIS OF CORRELATED NEURAL POPULATION ACTIVITY

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Spatiotemporal patterns of activity carried across large populations of neurons are the fundamental representation of information within the nervous system. Moreover, emerging evidence indicates that information processing in both the network and single-neuron levels are highly dependent on the pair-wise correlation structure of spike trains.

In this talk, I will describe new physical and computational tools aimed at allowing controlled emulation of correlated network activity patterns that we are developing towards a next-generation retina neuroprosthetic, as well as for basic-science applications. First, I will describe the development of rapid holographic stimulation systems capable of artificially controlling increasingly complex spatiotemporal activity patterns in neural populations with single-cell resolution. Next, I will describe a new *correlation distortion* computational strategy for exactly controlling the pair-wise correlation structure (defined in terms of auto- and cross-correlation functions) in multiple synthetic spike trains. Finally, I will show how this framework has been adapted to allow the identification of neural systems strictly from their correlation structures and highlight the possible application of blind identification in BMI research.

# MOLECULAR AND CELLULAR MECHANISMS OF MEMORY ALLOCATION IN NEURONAL NETWORKS

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The mechanisms that determine how information is allocated to specific regions and cells in the brain are fundamentally important for memory capacity, storage and retrieval, but are poorly understood. Our laboratory has manipulated CREB in a subset of lateral amygdala (LA) neurons with a modified Herpes Simplex Virus (HSV), and reversibly inactivated transfected neurons with the Drosophila allatostatin G-protein-coupled receptor (AlstR)/ligand system. We found that inactivation of the HSV-CREB subpopulation of neurons with allatostatin (AL) during training disrupted memory for tone conditioning, while inactivation of a similar proportion of HSV-LacZ control neurons did not. Whole-cell recordings of fluorescently tagged HSV-CREB neurons revealed that neurons with higher CREB levels are more excitable than neighboring neurons, and show larger synaptic efficacy changes following conditioning. These studies are currently being complemented with Channel Rhodopsin techniques in the lateral amygdala designed to activate the neurons engaged in fear conditioning. Our findings demonstrate that CREB modulates the allocation of fear memory to specific cells in lateral amygdala, and indicate that neuronal excitability plays a key role in this process.

# DISTRIBUTED PROCESSING AND TEMPORAL CODES IN CORTICAL NETWORKS

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The cerebral cortex presents itself as a distributed dynamical system with the characteristics of a small world network. The neuronal correlates of cognitive and executive processes often appear to consist of the coordinated activity of large assemblies of widely distributed neurons. These features require mechanisms for the selective routing of signals across densely interconnected networks, the flexible and context dependent binding of neuronal groups into functionally coherent assemblies and the task and attention dependent integration of subsystems. In order to implement these mechanisms, it is proposed that neuronal responses should convey two orthogonal messages in parallel. They should indicate (i) the presence of the feature to which they are tuned and (ii) with which other neurons (specific target cells or members of a coherent assembly) they are communicating. The first message is encoded in the discharge frequency of the neurons (rate code) and it is proposed that the second message is contained in the precise timing relationships between individual spikes of distributed neurons (temporal code). It is further proposed that these precise timing relations are established either by the timing of external events (stimulus locking) or by internal timing mechanisms. The latter are assumed to consist of an oscillatory modulation of neuronal responses in different frequency bands that cover a broad frequency range from 2 Hz (delta) to 40 Hz (gamma) and ripples. These oscillations limit the communication of cells to short temporal windows whereby the duration of these windows decreases with oscillation frequency. Thus, by varying the phase relationship between oscillating groups, networks of functionally cooperating neurons can be flexibly configurated within hard wired networks. Moreover, by synchronizing the spikes emitted by neuronal populations, the saliency of their responses can be enhanced due to the coincidence sensitivity of receiving neurons in very much the same way as can be achieved by increasing the discharge rate. Experimental evidence will be reviewed in support of the coexistence of rate and temporal codes. Evidence will also be provided that disturbances of temporal coding mechanisms are likely to be one of the pathophysiological mechanisms in schizophrenia.

# CROSSMODAL DEVELOPMENTAL PLASTICITY: LEARNING TO MATCH SOUND AND VISION

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For organisms to function successfully in the world they must be able to receive and process sensory information from external sources, and then respond with the appropriate action. Crucial to this process is the mammalian superior colliculus (SC), a sensorimotor structure that controls and directs orienting movements to external stimuli regardless of their sensory modality.

Previous studies have indicated that signals from the visual system are used to guide the formation of the topographic representation of auditory space. The site of plasticity for this cross-modal calibration of the auditory map in mammals is not known, but there are several indications that this is likely to be within the SC itself. So far, very little is known about the circuits that support the integration of the two modalities in the SC. Investigating the synaptic connectivity of these converging sensory inputs is a crucial step toward understanding both how sensory signals are transformed to motor commands and how vision calibrates the auditory space map during development. To do this, it is important to be able to study not only the output of multisensory neurons as manifested in their spiking patterns, but also the integration of subthreshold inputs.

We have investigated multisensory convergence and synaptic integration within the SC, using an in vitro slice preparation in rats and ferrets. We show that it is possible to use this preparation to stimulate auditory inputs to the dSC arising from the nucleus of the brachium of the inferior colliculus (nBIC) and visual inputs from the sSC, and to record the subsequent EPSPs in dSC neurons in a whole-cell patch clamp configuration. Locally converging circuits were found to be extensive and direct and synaptic inputs from sSC are topographically organized already before the onset of experience, suggesting a possible substrate for the experience-dependent alignment of the auditory space map. In addition, we show that the two inputs appear to be both spatially and temporally independent of each other (at least at subthreshold level), and thus interactions are likely to be mediated through overall level of activity of postsynaptic cell. Finally, we show that we are able to induce long lasting modifications in synaptic efficacy by manipulating patterns of electrical activity at these synapses.

We also investigated the intrinsic firing patterns of neurons in the dSC of the ferret with a view to developing an in vitro classification scheme for them. We found that the well-known WFV neurons, which exhibit unique anatomical features as well as the presence of the Ih current, could also be classified by means of their distinctive spiking pattern. The remainder of dSC neurons in our sample were successfully classified into two different groups by using multiple characteristics derived from their spiking patterns, in conjunction with the use of a quantitative cluster analysis technique.

Taken together, these data provide the first detailed intracellular analysis of convergent sensory inputs onto dSC neurons and form the basis for further exploration of multisensory integration and developmental plasticity.

# POSTER ABSTRACTS

# (in alphabetical order by first author)

# CHOLINERGIC DEPENDENCE OF A COGNITIVE TASK

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Acetylcholine (ACh) is a neurotransmitter implicated in several cognitive functions and is believed to especially affect the acquisition of new information. Learning adapts behavior to new situations and to new categories of stimuli.

We have examined the effects of scopolamine, an antagonist of muscarinic ACh receptors, on object categorization. Extensive behavioral pharmacological studies were carried out in two macaques. Performance was disrupted following injections of scopolamine. When the stimuli presented were novel, ie. when they had not been seen before the experiment, scopolamine significantly impaired performance in the categorization task. The monkeys were less impaired in categorizing a set of familiar stimuli, ie. stimuli that they had categorized successfully in previous sessions. Performance also deteriorated as the stimulus became less salient by an increase in the level of visual noise.

One of the questions of the role of cholinergic neurons in networks involved in the learning of new stimuli and in the performance of the categorization task is the type of information that they convey. Our recordings are aimed towards making the study of information in these networks feasible through simultaneous recordings of several neurons during the performance of a complex behavioral task requiring responses to a series of discrete stimuli at parametrically varied salience levels, belonging to two categories and two familiarity levels.

In addition to the behavioral experiments, neuronal activity was recorded in one monkey during a fixation task in which the monkey was presented with stimuli belonging to two categories. Preliminary recordings of neuronal ensembles have been made using tetrodes or polytrodes in the putamen, globus pallidus and nucleus basalis. All these regions have cholinergic neurons. Whereas cholinergic neurons in the basal ganglia are interneurons involved in local networks, their role is likely to be important as the basal ganglia are a crucial component in a circuit that underpins learning of conditional tasks. The nucleus basalis and other regions of the basal forebrain, on the other hand, have cholinergic neurons that project to the amygdala, hippocampus and cerebral cortex and are considered essential components in a variety of cognitive behaviors, including the formation of new memories. Neurons in the putamen had no visual responses but they anticipated the reward at the end of each trial. Neurons in the globus pallidus and the nucleus basalis were also reward predicting but could have in addition visual responses. These responses are related to the task performed by the monkey and may be important in the performance of the categorization task, in which case the prediction would be that the responses would be affected when categorization is impaired by scopolamine.

# DESIGNING OPTIMAL STIMULI TO CONTROL NEURONAL SPIKE TIMING

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We have developed fast, real-time implementable computational methods for optimally designing a natural or artificial stimulus to make a neuron emit a desired spike train. We consider three specific examples of artificial stimulation methods: intracellular and extracellular electrical stimulation, two-photon uncaging of caged neurotransmitters, and optical activation of genetically implanted light-sensitive ion channels. We also consider the case of optimizing a sensory stimulus (e.g., the spatiotemporal modulation of visual contrast, or the spectrotemporal modulation of sound) for this purpose. We discuss the close connection of this case to fast methods we have developed elsewhere for optimal Bayesian decoding of sensory stimuli. We adopt a model based approach, using relatively simple biophysical models which describe how, in the case of each stimulation method, the input affects the spiking activity of the neuron. For example, in the case of photo-stimulation of light-sensitive ion channels, we model how laser light interacts with the ion channels in a neuron and how the latter affect its membrane potential and hence its spiking activity. Depending on the type of the neuron in question, we have used both a conductance based leaky integrator model, and a resonator model inspired by a certain linearization of the Hodgkin-Huxley equations, to describe the membrane potential dynamics. Finally, in the case of sensory stimuli, we use a generalized linear model to effectively capture how the whole upstream sensory network encodes the stimulus in the spike train of the neuron in question.

Based on these models, we solve the reverse problem of finding the best time-dependent modulation of the input that makes the neuron emit a spike train which with highest probability will be close to a target spike train. However, this problem as stated is ill-posed: for example, if we can inject any arbitrary current into a cell, we can simply make the cell fire any desired pattern. Instead, we need to impose constraints on the set of allowed stimuli, as there are limitations on the stimuli we can safely apply in any physiological preparation without damaging the cells or causing other unwanted results. Thus, the task becomes a constrained convex optimization problem. We have developed fast methods for solving such optimization problems (Paninski et al. 2009). These methods can be implemented in real time and are also potentially generalizable to the case of many cells without losing tractability. This makes them suitable for neural prosthesis applications.

Our simulations show that our methods provide an automatic, fast, and stable way of constructing the best possible input. These simulations allow us to gauge how precisely spike trains can be induced in practice, given realistic values for the constraints such as the maximum allowed current, light intensity, etc. We have also experimentally tested the intracellular current injection method on pyramidal cells in mouse cortical slices. We see that the method is highly successful, achieving sub-milisecond spike timing precision and very high reliability with the current constrained to be within physiologically safe bounds. We are also in the process of experimentally testing the extracellular current injection and the neurotransmitter uncaging methods on neurons in cortical slices. Our work is motivated by several possible applications in neuroscience. As an example, our method can be used to produce desired spike trains in a number of selected neurons in some network. Observing the effect of the produced spikes on the subsequent activity in the whole network can then help study its connectivity patterns.

# CODING SIGNAL STRENGTH BY CORRELATED ACTIVITY IN BURSTING NEURONS

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Understanding how populations of neurons encode sensory information is of critical importance [1]. Correlations between the activities of neurons are ubiquitous in the central nervous system and, although their implications for encoding and decoding of sensory information has been the subject of arduous debates, there is a general consensus that their effects can be significant [2]. As such, there is great interest in understanding how correlated activity can be regulated. Recent experimental evidence has shown that correlated activity amongst pyramidal cells within the electrosensory lateral line lobe (ELL) of weakly electric fish can be regulated based on the behavioral context: these cells modulate their correlated activity depending on whether the fish is performing electrolocation or communication tasks without changing the mean firing rate of their response [3]. Moreover, it was shown in the same study that the changes in correlated activity were correlated with changes in bursting dynamics.

In this work we explore the role of intrinsic bursting dynamics on the correlated activity of ELL pyramidal neurons. We use a combination of mathematical modeling as well as *in vivo* and *in vitro* electrophysiology to show that bursting dynamics can significantly alter the ability of neuronal populations to be correlated by common input. In particular, our model predicts that the ratio of output to input correlations (i.e. the correlation susceptibility [4]) is largely independent of stimulus amplitude when neurons are in the tonic firing model. In contrast, we find that the correlation susceptibility increases with stimulus amplitude when the neurons are in the bursting mode (Fig. 1). We then performed *in vivo* and *in vitro* experiments to verify this prediction. Our results show that intrinsic dynamics have important consequences on correlated activity and have further revealed a potential coding mechanism for stimulus amplitude through correlated activity.

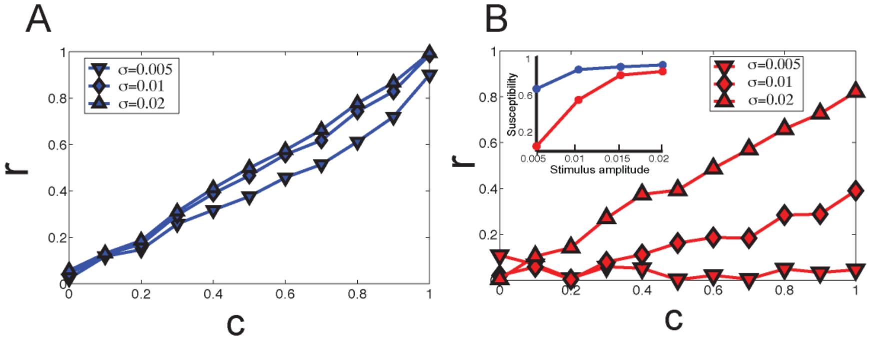

Figure 1. Modeling results: Output correlation coefficient, *r*, as a function of input correlation, *c*, for three different stimulus amplitudes in tonic firing neurons A and bursting neurons B. As shown in the inset the correlation susceptibility (i.e. the ratio of output correlation *r* to input correlation *c*) is roughly independent of stimulus amplitude *σ* when the neurons are in the tonic firing mode but increases with stimulus amplitude when the neurons are in the bursting firing mode.

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# POPULATION CODING PRINCIPLES IN THE SUPRAGRANULAR LAYERS OF THE MOUSE AUDITORY CORTEX INVESTIGATED BY TWO-PHOTON *IN VIVO* CALCIUM IMAGING

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Sound encoding in the auditory cortex has been mostly studied in paradigms where the response properties of a given neuron are considered independently of surrounding neurons. Hence, little is known about the coding properties and information content of neuronal ensembles. To address this question, we performed *in vivo* calcium imaging with single cell resolution using two-photon microscopy in isoflurane anesthetized mice.

Fields of neurons were bulk-loaded with the calcium indicator Oregon Green Bapta 1 (OGB1). We achieved simultaneous recordings of 40 to 100 individual cortical layer 2/3 cells using user-defined 2D line scans in a 200 x 200 µm area at a sampling rate of ~30 Hz. Typical calcium signals consisted of large (10–50% increase), clearly identifiable transients. We assessed the relationship between these transients and spiking activity of the neurons using combined imaging and single cell loose-patch recordings *in vivo*. Our measurements indicated that a single spike generated only a ~2% elevation of OG1 fluorescence which could not be reliably separated from measurement noise. However, fluctuations of the instantaneous firing rate could be well estimated from the temporal deconvolution of the calcium signal. The efficiency of this approach had been shown previously in the fish olfactory bulb but not yet in mammalian cortical neurons.

To investigate the coding properties of local layer 2/3 neuronal populations, we used a large set of sounds ranging from short (50 ms) pure tones or more complex arbitrary sounds to longer (2 sec) and temporally patterned sounds. We explored the hypothesis that different sounds could be encoded by differential population activity patterns occurring reliably upon each sound presentation. We assessed the degree of reliability from the correlation between single trial population patterns. In most recorded populations, a fraction of the presented sounds yielded reliability levels clearly above the chance levels. Reliable patterns could be observed from the onset up to 500 ms after presentation of short sounds. Long complex sounds elicited reliable patterns only during short epochs of the sound presentation. The position of these epochs as well as the sounds eliciting reliable responses varied from population to population. Generally, the overall trial to trial reliability of population activity was rather low (mean correlation ~0.2, while chance level is close to 0) although our data set also includes few highly reliable response patterns (mean correlation ~0.7). In addition, patterns elicited by different sounds were often overlapping and difficult to discriminate on a single trial basis, indicating that the activity of a local layer 2/3 neuron population provides only a limited amount of information about the set of sound tested.

These results show that population activity patterns within few tenths of neurons in the superficial layer of the auditory cortex can serve as a basis for sound encoding, but that the typical scale at which the cortical network may form fully discriminative representations of sounds might be much larger.

# HIGH-FIDELITY CODING WITH CORRELATED NEURONS

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Positive correlations in the activity of neurons are widely observed in the brain. As yet, these were believed to be detrimental to the fidelity of neural population codes or at best marginally favorable compared to coding with an independent population of neurons. Here, we show that positive correlations can enhance the coding performance of a neural population by astronomical factors. Specifically, the probability of a discrimination error can be suppressed by tens of orders of magnitude. This does not necessitate unrealistic values of parameters, but occurs for moderate values of correlations (of about 10 to 30%) and for populations with no more than a few tens of neurons. In fact, in the presence of correlation, reliable coding can occur even in cases in which individual neurons vary their responses so subtly with the stimulus so as to render coding with independent neurons impossible. The same mechanism which suppresses discrimination errors allows for a boost in capacity: a correlated population can encode an astronomically larger number of stimuli than an independent population. We estimate this number and demonstrate that it grows with the degree of response heterogeneity present in the population. Error suppression and capacity enhancement rest upon a class of correlation patterns. We discuss the nature of these patterns and suggest experimental tests to identify them.

# SPATIO-TEMPORAL COUPLING BETWEEN NEURAL ACTIVITY AND BOLD RESPONSE IN PRIMARY VISUAL CORTEX

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Neural activity in the brain is correlated with the blood-oxygen level dependent (BOLD) contrast which can be measured non-invasively by functional magnetic resonance imaging (fMRI). Up to date, many fMRI analysis methods are based on simplifying assumptions about the BOLD signal. Two popular assumptions are spatial independence and homogeneity of the haemodynamic response function (HRF) across voxels. As single voxels usually are not independent and moreover also exhibit different haemodynamic response characteristics, these assumptions might lead astray interpretations of fMRI data.

In this study we present an analysis framework that reveals the spatio-temporal correlation structure between simultaneously measured intracortical neurophysiological activity in primary visual cortex of the non-human primate and BOLD response. Given the spectrograms of neurophysiological activity and the simultaneously recorded BOLD data we compute a spatio-temporal convolution that links the activity measured at the electrode to the multivariate BOLD response. The convolution can be interpreted as the pattern in time-voxel space that reflects best the neural activity as it maximises the *canonical correlation* [1] between neural and haemodynamic activity.

Inspection of the estimated time-voxel patterns yields new insights in the spatio-temporal dependency structure of neurovascular coupling mechanisms. This study thereby extends previous results reported in [2,3], where the convolution was a time-frequency convolution estimated for the neurophysiological activity.

We show results from data collected during spontaneous activity and during visual stimulation. The analysis resulted in robust spatio-temporal coupling patterns across different experimental conditions. We compared the multivariate patterns with univariate coupling measures and spatial principal component analysis (SPCA), a popular method for connectivity analysis on fMRI data. Our findings suggest that neither univariate methods nor unimodal methods such as SPCA, which are based on autocorrelations of fMRI data only, can recover the multivariate spatio-temporal coupling structure in primary visual cortex.

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# TEMPORAL RESPONSE PROPERTIES IN AUDITORY CORTEX ARE DEPTH-DEPENDENT

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In the visual and somatosensory cortices, many neuronal response properties vary systematically across layers within a cortical column. These laminar differences have provided the foundation for theories about how cortical columns transform visual and somatosensory information. In the auditory cortex, however, few clear laminar differences in neuronal response properties have been found, complicating attempts to understand intracolumnar cortical processing of auditory information.

It has been suggested that temporal processing is a major function of the auditory cortex. We hypothesised that layer-dependence might therefore be most obvious for temporal response properties. To test this hypothesis, we recorded neuronal responses to short trains of noise bursts in the mouse primary auditory cortex (AI) and anterior auditory field (AAF). Responses of neuronal clusters were recorded simultaneously at different cortical depths using multielectrodes. Over 870 cluster recordings were obtained from a total of 118 penetrations in ten mice.

Following, quantified as the mean firing rate to second and later noise bursts normalised by mean rate to the first burst, was depth-dependent. Following was strongest in more superficial recordings, and weak in the deepest recordings even at slow presentation rates. Moreover, at mid-to-superficial depths in AAF, responses to later pulses in 2–4 bursts/s trains were augmented relative to the response to the first pulse. This augmenting response for 2–4 bursts/s trains was less pronounced in AI, and was not found in deeper layers in either area. We observed a different depth-dependence for neuronal excitability, which peaked at a depth presumed to correspond to layer V (Anderson et al., 2009).

These results demonstrate that there are systematic depth-dependencies in the temporal response properties of neuronal clusters within auditory cortical columns. It remains to be seen whether this arises from layer-dependent temporal response properties in single units, or layer-dependent changes in the composition of neuronal clusters.

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# NOT-SO-MOTOR CORTEX: TIMING DURING MOVEMENT PREPARATION

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Timing is a crucial aspect of motor behavior: the efficiency of movement preparation is greatly improved by reducing the uncertainty about when to move. What are the neuronal correlates of the influence of timing on motor preparation? Roux et al. (2003) showed that the delay duration modulates strongly the firing pattern of motor cortical neurons. Here, we were interested to know if the timing of events in a sensorimotor task influences the firing of motor cortical neurons in the absence of motor preparation. In other words, is motor cortex involved in non-motor, timing-related processes?

We trained two monkeys (*macaca mulata*) in a center-out pointing task in which the animals had to wait during two consecutive delays of equal duration. Each trial started with an auditory time cue (TC) indicating the duration of the two forthcoming delays: they can be either short (700 and 1000 ms, for monkey T and M, respectively), or long (1500 and 2000 ms). At the end of the first delay (D1), one of six peripheral targets was briefly lit as spatial cue (SC) and immediately masked by the onset of the 5 remaining targets. The presentation of SC was so short (55 ms) that the animal had to specifically attend in time its appearance for not missing it. During the second delay (D2), the animal had to memorize and prepare the movement indicated by SC. At the end of D2, the GO signal requested the execution of the movement. It is important to note that the two delays were conceptually different: D1 implied a visual detection task including attention in time, whereas D2 was a motor preparation task with a fixed foreperiod. While the monkeys performed the task, we recorded simultaneously the activity of up to 15 neurons in motor cortex (455 and 744 neurons in monkeys T and M, respectively).

Our data show that during D1, a pure non-motor delay, more than half of the neurons (70 and 57% in monkeys T and M, respectively) changed significantly their activity. These neurons include two types, defined by their firing pattern: delay-selective (DSel) and delay-sensitive (DSen) neurons. DSel neurons (4 and 17% in monkeys T and M, respectively), modulated their firing rate, whatever the delay duration. On the contrary, DSen neurons (42 and 28%) modulated their firing rate at the end of the short delay whatever the trial type. Even though only a small amount of DSel neurons were recorded in both monkeys, the mean firing rate of all neurons reflected significantly the DSel property in monkey M, but not in monkey T.

Based on these differences, we suggest that the two monkeys adopted two different attentional strategies to perform the task. Monkey M identified the delay duration from the beginning of the trial, based on the temporal information provided by TC, whereas monkey T waited for the end of the short delay to decide about the present trial type. We showed that the firing of motor cortical neurons can be strongly influenced by the task timing in a sensorimotor task, even in the absence of motor preparation. This could represent a pre-shaping of the motor network to receive the necessary motor information in a most efficient way.

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# INFORMATION ENCODING IN PREFRONTAL CORTEX BEFORE AND AFTER LEARNING TO PERFORM A COGNITIVE TASK

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The primate prefrontal cortex is essential for learning and performing cognitive operations. Little is known however about how learning itself affects information encoding in the prefrontal cortex. To address this question we recorded activity from prefrontal neurons of monkeys before and after they were trained to perform visual working memory tasks. Prior to training, the animals simply fixated while the stimuli that we eventually used in the tasks were presented passively. After training, the animals were required to remember the stimulus spatial locations and features and indicate if two stimuli presented in sequence were the same or different. Our experiments revealed differences in neuronal responses in the dorsolateral prefrontal cortex, defined by the two banks of the principal sulcus and the superior convexity (areas 8 and 46), and the ventrolateral prefrontal cortex which comprises the inferior convexity (areas 12 and 45). Approximately equal proportions of neurons in the dorsolateral prefrontal cortex were activated by the stimuli before and after training (37% vs. 39%). In contrast, the proportion of neurons activated after training increased significantly (from 9% to 21%). Regarding stimulus selectivity, training significantly *decreased* the percentage of neurons that were selective for the spatial location and features of stimuli, particularly in the dorsolateral prefrontal cortex. This result appears counterintuitive, considering that the monkeys were specifically trained to recall these stimuli. This result also stands in contrast with effects observed after perceptual learning, which typically sharpens neuronal selectivity. We used Receiver Operating Characteristic (ROC) analysis in a time-resolved fashion to determine how neuronal activity could discriminate between stimuli. This analysis indicated that all information regarding the discrimination of stimuli during either the interval of stimulus presentation or during the delay period was already present in neuronal responses prior to training. Learning to perform the task was associated with emergence of neuronal activity associated with more abstract information possibly related to task demands and rules. This new activity seemingly degraded the selectivity of neuronal responses for stimulus properties as the contrast to the best and worst stimulus properties diminished. Our results indicate that learning to perform a cognitive task is associated with different types of changes on two subdivisions of the lateral prefrontal cortex and we demonstrate a hitherto unknown effect of learning on neuronal information encoding.

# NEURAL ENCODING OF DECISION UNCERTAINTY IN THE PREFRONTAL CORTEX

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Uncertainty is ubiquitous in perception and decision making and makes inference particularly difficult (e.g. object categorization). Therefore, understanding how the brain represents and computes with uncertain information is a fundamental quest in neuroscience. Sensory data come with bottom-up uncertainty since they are corrupted by noise. Decisions are typically made by combining bottom-up sensory information with prior or top-down knowledge learned from the past. To achieve statistically optimal (or Bayes-optimal) behavior it is necessary for the brain to represent all these sources of uncertainty and combine them appropriately. Behavioral studies have demonstrated that humans perform close to Bayes-optimally when combining multiple sensory cues about an underlying stimulus, supporting the hypothesis that the brain represents and computes with probability distributions. However, the neural mechanisms used by the brain to compute under uncertainty remain elusive. We studied if top-down uncertainty was encoded in the prefrontal cortex. We have trained a monkey in a probabilistic classification task. The orientation of a stimulus (drifting grating) was drawn from one of two overlapping probability distributions. The animal had to infer from which class the stimulus came, although this could often not be determined with certainty. We recorded single-unit activity from the PFC using tetrodes while the monkey performed this task. We found that neurons not only encoded the class decision of the animal but PFC activity was also correlated with the posterior probability of class (i.e. class certainty). Specifically, neurons that preferred class A increased their firing when the probability of class A given the stimulus orientation was higher. PFC neurons also exhibited this effect during the delay period when the animal was required to remember its decision in the absence of the stimulus. Thus, we demonstrate that the PFC, a brain area thought to be at the peak of the decision-making hierarchy, encodes relevant probabilities associated with the inference problem the brain is solving.

# INTERACTION OF NEURAL CIRCUITS IN POSTERIOR PARIETAL CORTEX DURING A REACH AND SACCADE GATING TASK

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Neural circuits associated with planning reaches and saccades have been identified in the posterior parietal cortex. The lateral intra-parietal area (LIP) is involved with planning saccades while the parietal reach region (PRR) is involved in planning reaches. When eye and arm movements are coordinated, these circuits may interact. To link communication between movement plans with correlations in neural activity between area LIP and PRR, we have designed a Gating task. The logic of the Gating task is that if a reach plan is started, and if the goal of the reach is at the same location as the goal of a saccade that is already being planned, then existing information in the saccade plan could be used to plan the reach. A gating signal could turn on communication between saccade and reach plans. Studying the pattern of correlations between area LIP and PRR when saccade plans communicate with reach plans allows us to test the hypothesis that LIP-PRR coherence reflects the flow of planning information from the saccade circuit into the reach circuit. Single unit (SU) spiking, multiunit (MU) spiking, and local field potential (LFP) activity and the coherence between each was analyzed, as each gives us insight into different aspects of circuit dynamics.

Two monkeys were cued to first touch and fixate a central location on a proximal touchscreen. A red target cue then appeared at an eccentric location chosen to be within or opposite the receptive field for at least one cell or field under study. Since red targets were associated with eye movement goals, the monkeys planned a saccade. After a delay, each animal was usually cued to make a saccade alone to the target for a liquid reward. On a subset of trials, the color of the target changed from red to yellow after a variable delay. The color change signaled a change in plan from a saccade-alone to a combined reach and saccade. After a second variable delay, the go cue was presented, and each monkey made a look-and-reach.

We hypothesized that saccade planning activity should begin when the red target is presented and reach planning should start when the target color changes, but should depend on the strength of the on-going saccade plan. Analyses of both monkeys' behavior supported this hypothesis. The pattern of saccade and reach reaction times indicate that saccade plans do influence reaches. The more time each monkey has to plan a saccade before a cue changes, and hence the stronger the saccade plan, the faster the reaction time of the subsequent reach.

We simultaneously recorded SU, MU and LFP activity in area LIP and PRR to study changes in mean activity and coherence between activity in each area following the change in plan. A preliminary analysis of the LFP data indicates that during the delay period, the power of LFP activity at gamma and beta frequency bands predicts the reaction time of saccade and reach movements. LFP coherence between LIP and PRR around 20 Hz also predicts the average reaction time of combined eye-arm movements. Interestingly, we also find strong coherence between LIP and PRR when saccades-alone are being planned, but the degree of coherence does not predict movement reaction times.

These results suggest that neuronal coherence may encode the degree to which neural circuits between LIP and PRR are interacting to coordinate movement plans.

# NEURAL CODING OF CORRECTIVE MOVEMENTS IN MOTOR CORTEX

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It has been proposed that during a target switch reaching paradigm, the neural activity from motor cortex for the movement from starting point A to the original target B (AB) is replaced after the target switch with the neural activity for the motion from A to the new target C (AC). It is also known that the velocity profile for the target switch resembles the vectorial summation of the original AB velocity profile with that of the movement from original target B to the new target C (BC). Therefore, we considered the original as well as two competing hypotheses for neural coding of a target switch from B to C: (1) that coding for AB is replaced with AC, (2) that coding for AB is replaced with BC, and (3) that coding reflects the vectorial summation of the kinematics AB+BC.

We recorded neural activity from primary motor, dorsal premotor, and vental premotor cortices in one rhesus macaque performing elbow flexion/extension movements between five targets. These control trials were pseudorandomly interleaved with target switch trials, where the target jumped to a new location after the start of the original movement. This required a second, corrective movement to be planned and executed in order to successfully acquire the new target. We found that hypothesis (2) - AB replaced with BC - explained the neural data significantly better than the two alternatives.

We interpret this as evidence for “intermittent” motor control, whereby movement is constructed from a basis set of movement primitives or templates, because the planning of the corrective motion began with the endpoint of the original motion. Additionally, the neural activity is not simply a linear function of the kinematics, as predicted by hypothesis (3). Instead, neurons seem to exhibit a dramatic state change when the corrective motion is planned. This is potentially relevant for the design of brain machine interfaces, whose decoding algorithms often assume that neuronal activity is a linear function of the kinematics.

# DECORRELATED FIRING IN CORTICAL MICROCIRCUITS

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Correlated trial-to-trial variability in the activity of cortical neurons is thought to reflect the functional connectivity of the circuit. Many cortical areas are organized into functional columns, in which neurons are believed to be densely connected and share common input. Numerous studies report a high degree of correlated variability between nearby cells. We developed chronically implanted multi-tetrode arrays offering unprecedented recording quality to re-examine this question in primary visual cortex of awake macaques. We found that even nearby neurons with similar orientation tuning show virtually no correlated variability.

In a total of 46 recording sessions from two monkeys, we presented either static or drifting sine-wave gratings at eight different orientations. We recorded from 407 well isolated, visually responsive and orientation-tuned neurons, resulting in 1907 simultaneously recorded pairs of neurons. In 406 of these pairs both neurons were recorded by the same tetrode.

Despite being physically close to each other and having highly overlapping receptive fields, neurons recorded from the same tetrode had exceedingly low spike count correlations ($r_{\mathrm{sc}} = 0.005 \pm 0.004$; mean ± SEM). Even cells with similar preferred orientations ($r_{\mathrm{signal}} > 0.5$) had very weak correlations ($r_{\mathrm{sc}} = 0.028 \pm 0.010$). This was also true if pairs were strongly driven by gratings with orientations close to the cells' preferred orientations.

Correlations between neurons recorded by different tetrodes showed a similar pattern. They were low on average ($r_{\mathrm{sc}} = 0.010 \pm 0.002$) with a weak relation between tuning similarity and spike count correlations (two-sample *t* test, $r_{\mathrm{signal}} < 0.5$ versus $r_{\mathrm{signal}} > 0.5$: $P = 0.003$, $n = 1907$).

To investigate whether low correlations also occur under more naturalistic stimulus conditions, we presented natural images to one of the monkeys. The average $r_{\mathrm{sc}}$ was close to zero ($r_{\mathrm{sc}} = 0.001 \pm 0.005$, $n = 329$) with no relation between receptive field overlap and spike count correlations. We obtained a similar result during stimulation with moving bars in a third monkey ($r_{\mathrm{sc}} = 0.014 \pm 0.011$, $n = 56$).

Our findings suggest a refinement of current models of cortical microcircuit architecture and function: either adjacent neurons share only a few percent of their inputs or, alternatively, their activity is actively decorrelated.

# CAPTURING SLOW CONTRAST ADAPTATION OF RETINAL GANGLION CELLS WITH A GENERALIZED LINEAR MODEL

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Neurons throughout the visual system adapt to the statistics of visual inputs. In particular, the spike rates of retinal ganglion cells (RGCs) adapt to changes in luminance and contrast over several seconds (Smirnakis et al. 1997; Chander & Chichilnisky 2001; Baccus & Meister 2002). This observation is rarely accounted for in functional models of RGC response. The class of generalized linear models (GLMs) is easily fit to spiking data and can effectively characterize primate RGC responses to white noise (Pillow et al., 2008), but its ability to explain adaptive responses to non-stationary stimuli remains unexplored.

To address this question, we recorded macaque parasol RGC responses to a highly non-stationary stimulus consisting of a Gaussian signal modulated by a log-normal contrast envelope with spatiotemporal correlations matched to those of natural scenes (Frazor & Geisler 2006). Figure 1 shows an example frame of this stimulus. In a GLM, a neuron's instantaneous firing rate is modeled as the exponentiated linear combination of time-varying explanatory variables such as the stimulus and spiking history (Truccolo et al., 2005) of itself and any afferents. We parametrized the GLM to allow long time scale effects of spiking history (up to six sec), and fit the model by maximizing the likelihood of the data.

We cross-validated the fitted model on repeated stimuli with the same non-stationary statistics and found that the predicted PSTH's matched the true PSTH's (average of 0.76 and 0.83 correlation for 20 ON and 85 OFF cells, respectively). We also examined predicted responses of the same fitted model to a contrast-switching stimulus known to induce slow contrast adaptation (Smirnakis et al., 1997; Fairhall et al., 2001). Despite the difference between fitting and test stimuli, the model exhibited slow contrast adaptation that matched that observed in the corresponding cells responses (see Figure 2). The fitted model produces this behavior through a slowly decaying inhibitory effect of previous spikes.

We conclude that GLMs provide a flexible framework for capturing long time-scale behaviors such as slow contrast adaptation in RGCs. We are currently exploring the capacity of the model to explain other adaptive phenomena such as adaptation to naturalistic fluctuations in luminance and fast contrast gain control.

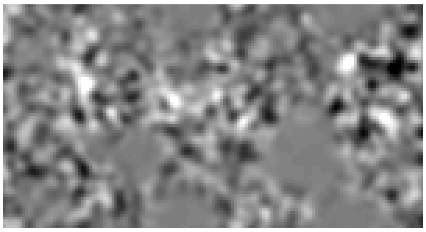

Figure 1: Non-stationary stimulus frame

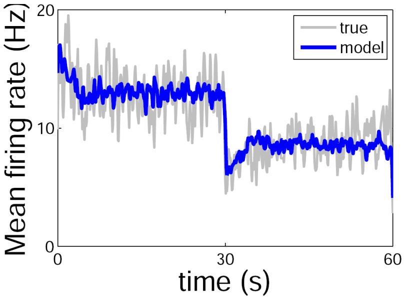

Fig. 2: Trial-averaged response of one cell to contrast-switching stimulus

# NORADRENERGIC MODULATION OF SPONTANEOUS ACTIVITY AND SENSORY-EVOKED RESPONSES IN PREFRONTAL CORTEX

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Neural coding in medial prefrontal cortex (mPFC) is thought to underlie various cognitive behaviors such as rule-guided learning, strategy use, or cognitive flexibility. Specifically, prefrontal neurons display many behaviorally relevant correlates related to sensory perception, motor responses, or reward that are believed to contribute to behavioral outcome. The mPFC is the cortical region that receives exceptionally dense dopaminergic (DA) innervation arising from the mesopontine Ventral Tegmental Area (VTA). Noradrenergic fibers originating from the brain stem nucleus Locus Coeruleus (LC) are also dense in mPFC. Previous investigations indicated that NA and DA systems have common target neurons in mPFC. The ascending NA and DA projections to mPFC have been implicated in a broad range of cognitive processes in rodents and primates including modulation of perception, attention, motivation, or memory. It is still, however, unknown whether and how NA and DA affect the prefrontal neural codes.

To address this question, we performed simultaneous recordings of unit activity and local field potentials in mPFC, VTA and LC in the rat. We first studied temporal relations of firing activity in the three brain regions during spontaneous and evoked activity under anesthesia. Mild electric shocks were applied to the rat hind paw for somatosensory stimulation. The LC neurons responded to a single foot shock (1ms, 5mA) with a short latency (~20ms), phasic burst, followed by brief inhibition. Trains of pulses (100ms, 50Hz, 5mA) elicited much stronger responses. The mPFC and VTA neurons did not respond to a single foot shock. Trains elicited sustained (~1s) excitatory responses in a subpopulation of mPFC neurons with latencies of ~100ms, usually followed by inhibition. Trains elicited both excitatory and inhibitory responses in a small number of putative dopaminergic, VTA cells, with latencies always greater than 100ms. Both spontaneous and evoked activity of VTA neurons was highly synchronized with mPFC activity; cortical activity always led VTA by several milliseconds. In some cases, sensory stimulation resulted in entrainment of mPFC and VTA neurons in several cycles of slow oscillation. Next, we inhibited the LC by systemic or local application of clonidine, an α2-adrenergic receptor agonist. This manipulation dramatically abolished the excitatory evoked responses in both VTA and mPFC without having much effect on spontaneous activity.

The results indicate that short-latency responses of LC neurons to somatosensory stimulation with corresponding release of NA modulate sensory responses in the target regions including mPFC and VTA. The long-latency responses of the VTA cells suggest that its ascending projections do not play an important role in modulating mPFC responses to noxious stimuli. VTA activity is rather driven by mPFC and, possibly, modulated by LC.

We will further investigate NA modulation of mPFC codes in the rat performing a prefrontal-dependent task. To induce release of NA in mPFC, we will apply electrical microstimulation to the LC just before presentation of discrimination stimuli, mimicking the burst activity of LC typically observed in response to salient stimuli. We expect to see more robust coding in the mPFC correlated with better behavioral performance in the presence of LC activation.

# ROLE OF SPECTROTEMPORAL MATCHING IN ENCODING INTERAURAL TIME DIFFERENCE

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Interaural time difference (ITD) is a principal cue for the horizontal position of a sound source. Jeffress (1948) proposed a circuit consisting of delay lines and coincidence detectors for encoding ITD that has dominated thinking about processing ITD. However, recent evidence brings the Jeffress account into question (Brand *et al.,* 2002). At a functional level, ITD-sensitive neurons have been characterized as performing a running cross-correlation of their effective inputs (Yin and Chan, 1990; Fischer *et al.,* 2008). Running cross-correlation can be derived from coincidence detection (Licklider 1957) and is thus consistent with the Jeffress model. A possible deviation from the Jeffress model is differences in frequency tuning of monaural inputs to coincidence detectors. If the inputs' best frequency (BF) differs, ITD tuning may become determined by cochlear delays (Shamma *et al.,* 1989). Previous studies have found that BFs of monaural inputs match in avian coincidence detectors (Pena et al. 2001, Fischer and Pena, 2009). A critical feature in early auditory responses is the presence of a time-dependent frequency tuning (instantaneous frequency (IF) glide). An IF glide has been observed in impulse responses of mammalian auditory nerve fibers (Carney 1999) and local field potentials (LFP) in nucleus laminaris (NL) of the owl (Wagner *et al.,* 2009). Its role in encoding ITD is unknown.

Here, we examine the role of the IF glide in the impulse response of early auditory neurons for the encoding of ITD. Our approach consisted of three components: (1) we characterized IF glides in the impulse responses of single neurons in the owl's early auditory pathway, (2) we used a cross-correlation model to test a non-Jeffress mechanism for encoding ITD based on mismatched IF glides, and (3) we characterized IF glides in the monaural impulse responses of nucleus laminaris neurons in the owl to test the non-Jeffress mechanism.

Using reverse correlation analysis, we computed the impulse responses of single neurons in NL and fit them with gammatone, gammachirp, gabor, and gaborchirp functions. We found that the chirping filters, with a linear IF glide, best fit the impulse responses, consistent with previous analyses of the LFP in nucleus laminaris. In contrast to the LFP study, we found no significant difference between the fits provided by the gammachirp and gaborchirp filters. By modeling NL neurons as performing a cross-correlation of an input signal filtered by left and right gammachirp filters, we show that small mismatches in both the slope of the IF glide and the time constant of the filters can shift best ITD while keeping the BF of the left and right inputs matched. This model predicts that the ITD produced is proportional to the interaural difference in the filters' time constants and the sign of the ITD is equivalent to the sign of the interaural difference of the IF glide slopes. This mismatching of IF glides represents a possible non-Jeffress mechanism for encoding ITD. To test if this mechanism could apply to NL, we computed the left and right monaural impulse responses from responses to binaurally uncorrelated noise and fit them with gammachirp functions. We found high correlation between the parameters of the left and right impulse responses. Also, the relationship between best ITD of the neuron and interaural differences in parameters did not follow the prediction of the non-Jeffress mechanism based on spectrotemporal mismatching of inputs. This analysis provides further support to the Jeffress model of ITD encoding in the owl's auditory system and indicates that the monaural inputs to auditory coincidence detectors are matched for spectrotemporal tuning.

# EVIDENCE OF PROBABILISTIC INTERNAL REPRESENTATIONS IN THE CORTEX FROM MULTI-ELECTRODE RECORDINGS

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Recently, perceptual and learning processes have increasingly been characterized as statistical inferences using probabilistic internal models based on noisy and ambiguous sensory inputs. Behavioral studies showed that humans and animals can perform such inferences in a statistically optimal way in a large variety of tasks. However, these results raise the question of how cortical networks represent and make use of the probability distributions necessary to carry out such computations. We adopted a computational framework positing that stimulus evoked activity (EA) in sensory cortical circuits represents samples from a posterior distribution over interpretations of the sensory input. We showed that, as a consequence, spontaneous activity (SA) recorded in the awake animal in the absence of sensory stimulation has a functional role in such representations (*Fiser et al. TICS 2010*). Specifically, SA reflects the structure of the underlying network and computationally it represents the internal model of the environment defined as the distribution of a priori expectations about possible interpretations. Since the internal model needs to be adapted to the statistical properties of the environment, for example the internal model in the visual cortex to the properties of natural scenes, a directly testable prediction of this framework is that the distribution of SA and that of EA in response to typical inputs should be close to identical in the mature visual system.

We developed a new analytical method to investigate this question based on measuring the Kullback-Leibler divergence (KL) between the distributions of EA and SA, and tested the prediction on multi-electrode recordings of the primary visual cortex of freely looking ferrets. Multiunit data was analyzed from 14 awake ferrets between the age of P25 and P151 recorded with a linear array of 16 electrodes in four conditions: while the animal was watching a movie, random dynamic noise or drifting gratings of different orientations (EA), and while the animal was in complete darkness (SA). Neural data was discretized in 2ms bins, binarized, and a joint histogram over possible states of the 16 channels was constructed for each of the four conditions. We found that a) the distribution of EA for movies was very close to that of SA (less than 1.5% of the minimum coding cost) while for the other stimuli the difference was significantly higher, b) that this similarity increased significantly with visual experience, and c) that it was determined by a match between the spatial and temporal correlational structure of the activity patterns, rather than merely by preserved firing rates across conditions. We also found that classical theories of visual cortical function based on independence and sparseness were not supported by our data. These results are in agreement with the sampling-based framework of internal representations and suggest that these samples come from a probabilistic model of the environment that is gradually adapted to natural scene statistics by sensory experience as the visual system develops.

# NEURAL POPULATION CODE MODEL FOR PATTERN DETECTION

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The visual system initially encodes the retinal image in terms of its "basic" constituents. Subsequently these basic constituents are used to construct the complex visual percepts that allow us to perform visual tasks. This process is referred to as decoding. A multitude of psychophysical detection threshold measurements has previously been taken as evidence that visual encoding is performed by independent, linear, spatial-frequency tuned detectors, so-called channels. In this view, the decoding process in detection tasks is formalized simply as selecting the output of the maximally responsive channel.

However, the traditional channel model is at odds with recent neurophysiological findings: spatial-frequency tuned neurons in primary visual cortex are neither linear, nor independent due to squaring and gain-control mechanisms. Furthermore, ample evidence emphasizes that behavioural performance in perceptual tasks is mediated by pooling responses of multiple neurons, rather than only relying on the most responsive neuron.

Here we show that the crucial psychophysical findings that have led to the linear independent channel model can be explained even better by a population code model consisting of a neurophysiologically inspired encoding front-end, followed by a population-decoding stage that approximates optimal Bayesian decoding. We simulated V1 population responses using the normalization model of simple cells and found that a simple combination rule successfully predicts square wave detectability, summation of far-apart frequencies, as well as the complex changes in contrast sensitivity following pattern adaptation. Intriguingly, the statistical characteristics of the discharge of cortical neurons allow this near-optimal readout rule to be computed in a bottom-up way. This can in addition explain the remarkable resistance to stimulus uncertainty displayed by human observers performing contrast detection.

Importantly, thus, all the data hitherto believed to imply linear, independent psychophysical channels can be linked to well-understood and simple physiological nonlinearities using statistical decision theory as the bridge.

# REAL-TIME SUB-SECOND MEASUREMENT OF OXYGEN FLUCTUATION CAN INCREASE THE INFORMATION EXTRACTED FROM THE BRAIN FOR USE IN NEURAL PROSTHETIC SYSTEMS

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Neural Prosthetic systems (NPS) must be capable of producing accurate and high resolution movements to all locations in space. These systems must accurately decode multiple goals along multiple directions if they are to benefit the diverse population of paralyzed patients. Neurons in the medial intraparietal area (MIP) and the dorsal premotor cortex (PMd) have broad tuning curves that collectively define a limit of proximity (LOP) between two decodable targets. The LOP outlines the maximum distance from a target within which the decode algorithm can still accurately predict the location of that target. Adding electrodes may decrease the LOP but increases the risk to patients. We investigated information coding in the brain with the specific goal of decreasing the LOP. Here, we propose that neural learning and the ability to record from multimodal electrodes has the potential to greatly enhance information transfer rates without increasing the number of implanted electrodes. We recorded the electrical activity from the dorsal premotor cortex (PMd) and the electrical and local oxygen ($O_2$) fluctuation from MIP. The $O_2$ concentration was measured with a 100ms resolution using custom designed and fabricated highly sensitive $O_2$ sensors that were lowered through a guide tube 1 mm away from the metal electrode. Monkeys performed a center-out memory reach task to targets in the periphery to 2 different amplitudes per direction on a 2D fronto-parallel plane. Although we were able to accurately predict impending reaches along multiple directions, we encountered difficulty when decoding multiple goals along a single direction. Initially, we only found a small fraction of neurons that encoded amplitude. However, by manipulating reward, we found that amplitude tuning rapidly emerged in neurons with no previous amplitude encoding. We propose that this emergent encoding of variables represents optimization of reach networks that decode algorithms can translate into an enhanced LOP, improving spatial resolution. Oxygen recordings were obtained alongside acute single electrode recordings in monkeys performing reaches to 2 directions and 2 amplitudes per direction. The local $O_2$ signal also contained information about both amplitude and direction. Using this method we found that a single $O_2$ channel was differentially tuned for all 4 conditions (2 directions X 2 amplitudes) and yielded 67-98% successful decode, depending on the site of recording. In some cases, we obtained higher decode rates using the $O_2$ signal than using the local field potential and the neural activity from a single electrode. We are currently assessing the benefit of the $O_2$ signal on reducing the LOP. In addition, fluctuation in $O_2$ concentration preceded the activation of the local field potential and neural activity on many trials raising the possibility that the brain uses predictive mechanisms to increase the $O_2$ available in regions about to become active. We are currently investigating this early signal as a proxy for volition. We propose that deliberate training of neurons and the use of multimodal electrodes will greatly enhance the potential of NPS by providing a novel method for information extraction from the brain.

# INTERACTIONS BETWEEN PRIMARY MOTOR CORTEX AND SECONDARY OLFACTORY CORTEX DURING AN OLFACTORY-GUIDED DECISION MAKING TASK

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Many older studies of the neural basis of sensory-guided decision-making argued for a “tripartite view” of this process, in which sensory information is relayed to prefrontal (PFC) and basal ganglia (BG) circuitry, where a “decision” is made, and then motor planning and output take place if the decision involves action. More recent studies have shown that perceptual decision processes are reflected in, if not caused by, the activity across a much more distributed set of neural networks, including neurons in secondary sensory areas and possibly the primary motor cortex. Virtually all of these studies, however, have lacked neural measurements with high spatial *and* temporal resolution, and with the exception of one study, they have not taken advantage of recently developed, sophisticated signal analytical techniques allowing the detection of how neural circuits interact in the time and frequency domains. The most important shortcoming, we stress, has been the lack of an examination of how these distributed circuits *interact* to produce different behavioral outputs.

We tested whether the rat primary forelimb motor and secondary olfactory cortices sent behaviorally relevant signals to each other, likely via the PFC, during the putative PFC/BG decision-making period as rats performed an olfactory-guided GO/NO-GO task. The task required rats to execute a skilled reach to the target on GO trials and to freeze briefly on NO-GO trials. We obtained multi-site, multi-electrode recordings from these areas during early-stage and asymptotic task performance, and analyzed the neural data with an advanced information flow tracing technique, Granger causality, performed mainly on local field potential (LFP) data. We found that behaviorally relevant signaling patterns arose over the course of task learning between the two recorded sites. On asymptotically performed trials, just before the rats’ final sniff of either a GO or NO-GO target, the forelimb motor cortex sent a theta/beta band (~4–29 Hz) signal, which we termed a “query,” to the olfactory cortex. Then, *only* if the target was a GO-scented target, and only if the rat was performing significantly above chance in the task, the olfactory cortex “replied” to forelimb M1 with a beta band (12–29 Hz) signal, which was followed ~60 ms later by M1 paw lifting-associated unit activity and the lift of the reaching forepaw. The signaling patterns had behavioral relevance because they arose as animals learned the meaning of the GO and NO-GO cues; the olfactory beta-band “reply” only occurred on well-learned GO trials; and this beta-band signal predicted movement preparation and paw lifting. We conducted a second experiment to test whether the signals were more related to sensorimotor coordination and trajectory planning rather than the decision process *per se*, by performing Granger causality analyses on LFPs from well-learned, *correct GO trials* as well as well-learned, *incorrect NO-GO trials*, on both of which the rats attempted to grasp the targets. The signaling patterns on correct GO trials replicated the above findings, and the signaling patterns on incorrect NO-GO trials resembled those of correct, well-learned NO-GO trials, displaying a motor “query” but no olfactory→motor “reply.” Despite the lack this olfactory signal, animals’ grasped the targets with similarly high accuracy on correct GO trials and incorrect NO-GO trials, suggesting that the olfactory “reply” was not needed for accurate trajectory planning. We hypothesize that the olfactory beta-band activity signals to the prefrontal and forelimb motor cortices that the current cue is a GO cue, therefore *playing a crucial role in the decision process*. We further suggest that the motor “query” is a precursor to the motor cortex’s *providing constraints on the decision result space* to prefrontal and other circuitry, consistent with results of computer modeling studies. We are beginning to perform causal experimental manipulations to test these novel, specific hypotheses regarding sensory and motor cortices’ roles in decision making, as well as beginning to perform information flow analyses on our spike data.

# THE TIME SCALES OF INFORMATION REPRESENTATION IN AUDITORY CORTEX ARE STIMULUS DEPENDENT

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Recent work has shown that in auditory cortex acoustic stimuli are potentially encoded by different neural codes, each operating on different temporal scales. For example, the millisecond-precise timing of individual neuron's action potentials has been implicated similarly as firing rate modulations on slower scales or the timing of spikes to ongoing oscillatory background activity [1]. Here we asked whether the temporal precision of these putative neural codes is fixed and inherent to the system, or whether their temporal precision is determined by the acoustic stimulus.

Stimulus information in different codes was compared during stimulation with naturalistic sounds and sequences of random tones. The natural sounds had a typical autocorrelation of around 20–30 ms (computed from the envelope of individual frequency bands), while random tones had a much shorter autocorrelation time (around 10 ms). Neural activity was recorded using multiple electrodes in primary and secondary auditory cortex of macaque monkeys passively listening to these stimuli. Mutual information between stimulus and neural activity was characterized using previously established approaches [2,3].

We found that the precise time scale of each code depends on the acoustic stimulus. For binary spike words (spike timing), the temporal precision required to decode maximal information was higher during stimulation with random tones (average 7 ms) than with natural sounds (average 12 ms). In addition, the degree to which field potentials were stimulus locked ('entrained') varied between sound types: during stimulation with random tones entrainment was stronger and extended to much higher frequencies (up to 60Hz) than during stimulation with natural sounds (about 30 Hz).

These results extend previous finding in the visual thalamus and demonstrate that the temporal precision of sensory neurons responses in auditory cortex depends on the temporal structure of the stimulus. In particular, stimuli with shorter correlation times, hence faster intrinsic time scales, induce responses that vary on shorter time scales. This implies that the relevant time scales of neural codes are not fixed, but are dynamically adapted to, or reflect the environment.

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# MOTOR CORTICAL EVOKED LOCAL FIELD POTENTIALS ARE SENSITIVE TO VISUOMOTOR TASK TIMING AND PERFORMANCE, AND ARE MODIFIED BY LONG-TERM DAILY PRACTICE

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Evoked potentials are observed in motor cortical local field potentials during movement execution (Movement Related Potentials, MRPs), and in response to task-related visual cues (Visual Evoked Potentials, VEPs). Motor cortical evoked potentials may be directionally selective, but little is known concerning their relation to other aspects of motor behavior, such as the task timing and the behavioral performance.

To study motor cortical evoked potentials under different behavioral contexts, we recorded local field potentials from two macaque monkeys during execution of a pre-cued arm-reaching task in 6 directions. The task included two consecutive delays, which varied in duration from trial to trial in a pre-cued fashion. The available time for movement preparation and the overall pace of the task thereby varied from trial to trial, while the visual spatial cues and the required movements were the same in short and in long trials.

We observed systematic modulations in evoked potential sizes in relation to the task timing and the behavioral performance within sessions. We also observed long-term modifications in evoked potential sizes across months of daily practice in the visuomotor task.

In particular, VEPs in response to the spatial cue were systematically larger in short trials and MRPs around the movement were larger in long trials. This modulation due to the task timing interfered little with the preferred directions of significantly directionally selective VEPs and MRPs. We also found that the behavioral reaction time (RT) was positively correlated with MRP size and negatively correlated with VEP size, within sessions.

In parallel with the improvement in the behavioral performance across sessions (a decrease in RT and in the proportion of errors), there was a significant decrease in the size of VEPs and MRPs. The RT was therefore positively correlated with the evoked potential sizes across sessions.

Our results clearly show that apart from reflecting the specific movement parameters in the visuomotor task (e.g. movement direction), motor cortical population activity is strongly influenced by the behavioral context in which the movement is made. Our results also suggest a complementarity of early (VEP) and late (MRP) motor cortical activity during preparation and execution of trained arm movements, dynamically adapting to the behavioral context on a trial-by-trial basis. We conclude that local field potentials provide a sensitive measure of changes in the population activity, in relation to changes in the behavioral performance.

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# ANALYSIS OF FUNTIONAL CIRCUITRY IN PRIMARY VISUAL CORTEX OF AMBLYOPIC MONKEYS

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Amblyopia is a developmental disorder of vision that predominantly affects spatial visual processing. It is typically characterized by reduced acuity and contrast sensitivity of one eye. Single unit electrophysiological studies in primary visual cortex (V1) of amblyopic monkeys have found evidence for reduced acuity and contrast sensitivity of neurons driven by the amblyopic eye, but the neural deficits are not quantitatively sufficient to explain the behaviorally measured loss. This suggests that there are abnormalities in the amblyopic cortex that are not expressed in the responses of individual V1 neurons. One possibility is that the coordinated activity of populations of amblyopic eye neurons is somehow disrupted. To investigate the status of local circuitry in amblyopic V1, we studied the correlation structure among pairs of neurons in amblyopic monkeys.

We recorded from V1 of three anesthetized, paralyzed adult *Macaca nemestrina* using a 100-electrode array. Two animals had surgically-induced strabismus in infancy that resulted in deep amblyopia; the third was a visually-normal control. The array was implanted 0.6 mm into a portion of parafoveal V1, yielding superficial layer recordings. We presented identical sinusoidal grating stimuli of fixed, moderate spatial and temporal frequency separately to each eye; on different presentations the gratings drifted in one of twelve directions around the clock. From each electrode, we recorded all responses that exceeded a threshold and sorted these waveforms offline. We analyzed data only from well-isolated single neurons.

Responsivity was decreased substantially for stimuli presented to the amblyopic eye compared to the fellow eye. This decrease in firing rate was accompanied by a significant increase in correlated trial-to-trial response variability (“spike count correlation”). This may be explained by decreased behavioral and neural contrast sensitivity in the amblyopic eye, resulting in the identical stimulus having lower effective contrast. We found no difference in the magnitude of fine time scale synchronization of neuronal responses for stimuli presented to the two eyes, and the spatial extent of correlation on slow and fast time scales was similar in amblyopes and controls. However, the dependence of correlation on orientation tuning similarity was different between the eyes --- both slow and fast time scales of correlation were more restricted to similarly tuned neurons for the amblyopic eye. These eye-dependent differences were not found in the normal control. We conclude that the correlation structure of visually-evoked activity in V1, and therefore the underlying circuitry, is distinctly different in amblyopes. The abnormalities of amblyopic vision may, at least in part, be explained by these differences in the circuitry of V1.

# A HIGH-THETA RHYTHM OF FRONTO-POSTERIOR DIRECTION APPEARS DURING THE K-COMPLEX IN NREM STAGE II OF HUMAN SLEEP

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The K-complex (KC) is one of the most distinctive electroencephalographic elements of NREM stage II of sleep. It appears as a biphasic slow wave, of >500 msec duration, with a major frontal predominance, standing clearly out of the EEG background. Despite it being known and well described for more than 70 years (Loomis *et al.* 1938), the functional role of the KC is far from understood. Some consider it to be an arousing reaction to endogenous, mainly autonomic, stimuli (Roth *et al.* 1956). Others argue in favor of it being a sleep protecting mechanism (Colrain 2005) and forerunner of slow wave sleep delta activity (De Gennaro *et al.* 2000). More recently, a study investigating KC-spindle interactions revealed a high-theta or low alpha band (~8.82±1.20 Hz) short oscillation produced during the course of the KC (Kokkinos and Kostopoulos 2010).

This study investigates the features of the observed intra-KC high-theta oscillation. Seven healthy individuals spent a whole night sleeping in the lab, while EEG was derived from 58 electrodes along with EMG and EOG for REM verification. NREM stage II periods were identified and a total of 1444 KCs were selected for study. Based on the observation that the intra-KC oscillation might vary with KC duration, we grouped separately KCs with 2 (348/1444, 23.95%), 3 (308/1444, 21.78%) and 4 (52/1444, 4.10%) peaks of high-theta. We marked the second peak in all, high-pass filtered the signal at 4 Hz and performed topographic analysis in electrode space. In a significant proportion either no intra-KC high-theta was observed (293/1444, 19.39%) or it was difficult to determine a clear rhythmic activity (364/1444, 25.57%). A lesser proportion of KCs were covered by continuous alpha activity (79/1444, 5.58%).

In the majority (88.2%) of 2-peak oscillations, the first peak localized frontally and the second posteriorly in all subjects. In 85.7% of the 3-peak oscillations, the first peak appeared frontally, the second centrally and the third either parietally or occipitally, in 6/7 subjects. In the seventh subject, the second peak appeared posteriorly and the third centrally. In all 2- and 3-peak samples there was a minor percentage where the oscillation had posterior-frontal direction (38/348, 11.80% and 36/308, 14.30% respectively). KCs with 4-peaks of high-theta (52/1444, 4.10%) had a wider topographic variance across subjects, although they kept a systematic profile within subjects. In all subjects, while on average the intra-KC oscillation varied topographically as described above, the low-pass filtered at 4 Hz slow wave of the KC localized frontally on average, without indications of interlobular shifts.

We showed that the rhythmic activity often appearing during the time-course of the KC is an independent oscillation and not a part of the KC. Given that cortical activity has been shown to cease when KCs appear (Cash *et al.*, 2009), it is possible that this high-theta rhythm is generated by subcortical structures. In addition, the fact that this oscillatory activity lies at the limits of the theta and alpha band, the former a background feature of NREM stage I and the latter a band strongly correlated to arousals, suggests that this intra-KC oscillation might reflect mechanisms of the endogenous arousing stimulus the KC is protecting the cortex from.

# DISTINCT INTERNEURON CELL TYPES SHAPE PERSISTENT ACTIVITY PROPERTIES IN A PFC MICROCIRCUIT MODEL

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Neurons in the prefrontal cortex, both pyramidal neurons and interneurons, exhibit stimulus-selective firing that persists past the end of the stimulus (i.e. persistent activity), an activity pattern that underlies the on-line maintenance of a memory. Interneurons comprise the most numerous and diverse cells in the cortex and can be classified based on the calcium-binding proteins they express in parvalbumin (PV), calbindin (CB) and calretinin (CR) interneurons, having different connectivity and firing-pattern profiles. It has been suggested that the three interneuron subtypes contribute differentially to the emergence of persistent activity. Our goal is to identify the ways in which the different types of interneurons shape this sustained activity in a Prefrontal Cortex (PFC) model microcircuit.

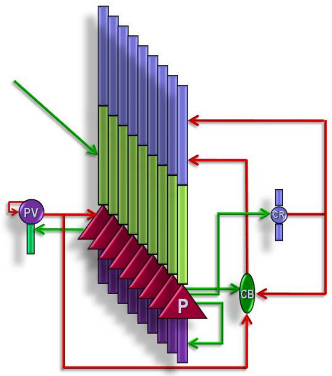

Fig 1. Network structure

Towards this goal, we modeled the three different types of interneurons present in the PFC using the NEURON simulation environment. All three interneuron models included the ionic mechanisms for the fast Na$^+$, fast K$^+$ and delayed-rectifier K$^+$ currents as well as other ionic mechanisms known to be present in each type. The PV model consisted of two compartments and included mechanisms for slow K$^+$ current ($I_{Ks}$), a type of high-threshold activated Ca$^{++}$ current (N-type), and the hyperpolarization-activated K$^+$ current ($I_h$) and exhibited very high frequencies. The CB model consisted of one compartment and included mechanisms for the low-threshold Ca$^{++}$ current (T-type) and the $I_h$ and exhibited a regular spiking behavior. The CR model consisted of three compartments and included mechanisms for $I_{Ks}$, fast Ca$^{++}$-activated K$^+$ current and N-type Ca$^{++}$ current and exhibited irregular firing behavior. We then constructed a twelve neuron microcircuit (9 pyramidal models, previously validated in our lab, and 3 different types of interneurons), in which the relative number of neurons and the connectivity profiles were validated against anatomical and electrophysiological data. Persistent activity in the model network was induced by an excitatory stimulus to the pyramidal models. The role of the three different interneuron models in persistent activity properties (firing frequency, synchronicity) was studied by simulating 'knock-out' networks for each interneuron subtype. In addition, the postsynaptic targets of each interneuron were altered, in order to dissect the contribution of the connectivity vs. the firing-pattern profiles of the different types.

We find that the PV interneuron shapes the firing frequency of the pyramidal neuron models during persistent activity, while somatic inhibition, regardless of the interneuron subtype, is crucial for maintaining synchronous firing of pyramidal models during persistent activity. These data suggest that balanced inhibitory inputs determine the properties of persistent firing and reinforce the idea that disruption of inhibitory-mediated regulation in PFC networks may underlie various forms of pathology.

# CAUSES OF FIRING IN CORTICAL NEURONS REVISITED: TEMPORAL INTEGRATION VERSUS COINCIDENCE DETECTION

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In this paper, we address the question of quantifying the relative contribution of temporal integration and coincidence detection to the high firing variability observed in cortical neurons [1]. Such a quantification of the two neuronal operational modes would be a significant step in shedding light to the underlying coding scheme, as substantially more temporal integration would suggest that information is encoded in the rate of the neuron's output spike train, while substantially more coincidence detection would indicate the importance of the timing of individual spikes in the encoding of information, pointing towards a temporal code.

In a previous attempt to identify the operational mode of the cortical neuron, Bugmann *et al.* [2] used reverse correlation (RC) graphs of the stimulus of a leaky integrate-and-fire (LIF) neuron model with the partial somatic reset mechanism (which has been shown to be the most likely candidate to reflect the mechanism used in the brain for reproducing the irregular firing of cortical neurons at high rates [2,3]). They were unable to provide a conclusive answer however (despite that RC graphs were recommended for such a purpose by Mainen and Sejnowski [4]), and they suggested that RC of the membrane potential may be more informative.

Based on this suggestion, in our current attempt to determine the operational mode of the cortical neuron, we use RC of the membrane potential of a LIF neuron with partial reset. Our algorithm employs a curve similarity metric to measure the similarity between the membrane potential time course preceding each spike with the reverse correlation of the membrane potential of a pure temporal integrator and a pure coincidence detector neuron. The outcome is a measure of the number of spikes caused by each operational mode, which indicates the relative contribution of each mode to the production of spikes in our model. Our preliminary results show that at firing frequencies from 70 Hz to 170 Hz the model operates mainly as a temporal integrator, while at firing rates between 170 Hz and 280 Hz, coincidence detection is the dominant mode. This is slightly different from other studies like the one by Goedeke and Diesmann [5], who demonstrated that the two modes cannot be distinguished. An alternative, analytical approach is also presented, which relies on analytical derivations of the RC graphs. Can our method above be adapted to determine whether ensembles of identical neurons follow the operational mode of the individual ones that comprise them, or if the network as a whole exhibits a different behaviour? This and other questions will be discussed at the conference.

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# WHAT IS THE GOAL OF COMPLEX CELL CODING IN V1?

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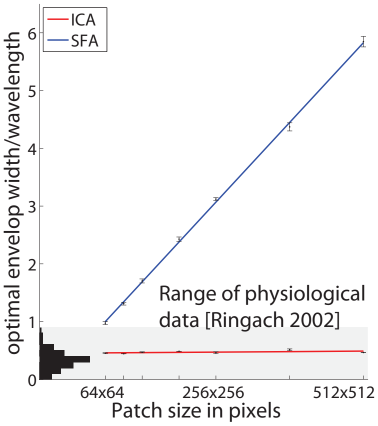
A long standing question of biological vision research is to identify the computational goal underlying the response properties of sensory neurons in the early visual system. Some response properties of visual neurons such as bandpass filtering and contrast gain control have been shown to exhibit a clear advantage in terms of redundancy reduction. The situation is less clear in the case of complex cells whose defining property is that of phase invariance. While it has been shown that complex cells can be learned based on the redundancy reduction principle by means of subspace ICA [Hyvarinen & Hoyer 2000], the resulting gain in redundancy reduction is very small [Sinz, Simoncelli, Bethge 2010]. Slow feature analysis (SFA, [Wiskott & Sejnowski 2002]) advocates an alternative objective function which does not seek to fit a density model but constitutes a special case of oriented PCA by maximizing the signal to noise ratio when treating temporal changes as noise.

Here we set out to evaluate SFA with respect to two important empirical properties of complex cells RFs: (1) locality (*i.e.* finite RF size) and (2) an inverse relationship between RF size and RF spatial frequency. To this end we use an approach similar to that employed by [Field 1987] for sparse coding. Instead of single Gabor functions, however, we use the energy model of complex cells which is built with a (quadrature) pair of even and odd symmetric Gabor filters. We evaluate the objective function of SFA on the energy model responses to motion sequences of natural images for different spatial frequencies and envelope sizes, with patch sizes ranging from 64×64 to 512×512.

We find that the objective function of SFA grows without bound for increasing envelope size (see Figure, blue line). Consequently, SFA by itself cannot explain spatially localized RFs but would need to evoke other mechanisms such as anatomical wiring constraints to limit the size of the RF. It is unlikely, however, that such anatomical constraints are able to reproduce the inverse relationship between RF size and spatial frequency.

In contrast to SFA, the objective function of subspace ICA yields a clear optimum for finite envelope sizes, regardless of assumed patch size (see Figure, red line). In particular, the optimum envelope size is inversely proportional to spatial frequency — just as observed for physiologically measured RFs in primary visual cortex of cat [Field & Tolhust 1986] and monkey ([Ringach 2002], histogram see Figure).



We conclude that SFA fails to reproduce important features of complex cells. In contrast, the envelope size predicted by subspace ICA lies well within the range of physiologically measured receptive field sizes. As a consequence, if we interpret complex cell coding as a step towards building an invariant representation, the underlying algorithm is more likely to resemble a sparse coding strategy as employed by subspace ICA than the covariance based learning rule employed by SFA.

# AN EXCITATORY ROLE FOR GABAERGIC INTERNEURONS IN 4-AP-INDUCED ICTAL EVENTS

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4-AP induced seizure-like events (SLE) in the entorhinal cortex require both GABAergic and glutamatergic neurotransmission. Here we use a recently developed laser-scanning strategy, Targeted Path Scanning (TPS), in conjunction with two-photon excitation of bath-applied, calcium-sensitive dye, Indo-1 AM, to image epileptiform activity in slices of hippocampal formation from GAD67-GFP (GIN) mice. In this way, we are able to record simultaneously activity in populations of GABAergic interneurons (I-cells) and putative excitatory neurons (E-cells). At 4-AP-induced SLE onset, we observed a high amplitude pre-ictal spike that is significantly larger in I-cells than it is in E-cells. Conversely, in SLEs induced by zero-Mg2+ solutions, there is no difference in amplitude between I-cells and E-cells. We hypothesize that, in 4-AP-induced SLEs, I-cells must fire hard enough to become depolarizing and alleviate the NMDA receptor Mg2+ blockade, whereas, in zero-Mg2+-induced SLEs, both I-cells and E-cells contribute to SLE generation from the beginning. Simultaneous dual patch recordings of GFP-expressing interneurons and putative E-cells reveal seemingly random firing before the pre-ictal spike. After the pre-ictal spike, however, E-cell spikes follow I-cell spikes by approximately 3ms, suggesting a monosynaptic, excitatory GABAergic connection (Fig. A). Furthermore, acetazolamide, a drug that blocks production of the depolarizing, GABA-synapse permeant ion, bicarbonate, reduces ictal activity in 4-AP, but not in zero-Mg2+. Finally, using Clomeleon mice, which express a genetically-encoded chloride sensor, we directly imaged a substantial increase in intracellular chloride at SLE onset (Fig. B). Together, these results suggest that GABA can have a significant excitatory modulatory effect that contributes to SLE generation through both the depolarizing actions of bicarbonate current and depolarization of the chloride reversal potential caused by breakdown of the chloride gradient.

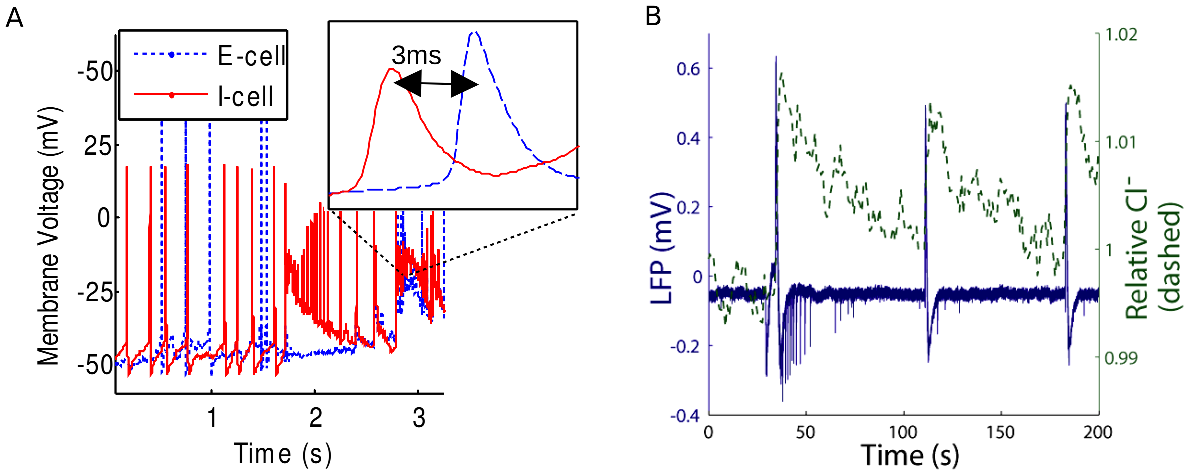

Figure: (**A**) I-cell (solid) and E-cell (dashed) spikes are asychronous prior to pre-ictal spike (1.7s) and precisely timed I-cell before E-cell following pre-ictal spike. (**B**) Sharp long lasting chloride increases (dashed) correspond to ictal-like activity in LFP (solid).

# LOW-COMPLEXITY DECODING IN INTRACORTICAL NEURAL INTERFACES FOR HUMANS WITH TETRAPLEGIA

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For people with tetraplegia secondary to spinal cord injury, ALS or brainstem stroke, intracortical neural interface systems have the potential to enable reliable communication and control of external devices such as a computer, robot arm or functional electrical stimulation device. Our ongoing pilot clinical trial of the BrainGate2 Neural Interface System has demonstrated the ability to acquire spiking activity from ensembles of single neurons in the motor cortex of clinical trial participants and decode these rich signals to produce the intended kinematics.

Thus far, we have used the Kalman filter for neural decoding, since it is computationally tractable and optimal for a large class of signal types. It may, however, may be too complex for real-time decoding of large-dimensional signal sets, such as those obtained from multiple intracortical recording arrays or comprising multiple signal types. For stationary systems, it is often possible to exploit the non-varying nature of the state space model coefficients and use a simpler decoder. We observe that the Kalman filter gain converges rapidly to a steady-state value, leading us to test whether a steady-state approximation to the gain, computed *a priori*, might be sufficiently accurate in addition to being lower in complexity.

We analyzed human neural spike signals from one data set acquired 1003 days after array implantation during a center-out task involving neural control of a computer cursor. The Kalman filter was trained with 6 min. of open-loop motor imagery data obtained from the same center-out task. Decoding the closed-loop data, we found that the optimal Kalman filter gain, which depends only on the system matrices and not the observations, converges rapidly to a steady-state value. This steady-state gain can be pre-computed offline using the Riccati equation, avoiding complex real-time gain computation. We found that the steady-state approximation introduces a negligibly small difference to the estimated kinematics during the first few seconds, after which the estimates are identical. The steady-state approach, applied to decoding 10 min. of spike data from 29 neurons, decreased the program execution time on our platform from 23 sec. to 0.5 sec., which is a 40-fold increase in computational efficiency.

Such a substantial improvement in efficiency, even for relatively simple neural spiking data sets, is valuable for the implementation of both online neural control tasks and offline performance analyses. As complex algorithms require sophisticated digital hardware with high energy consumption, our technique will ease those requirements and will be particularly valuable for fully-implantable wireless interfaces, which we are also currently developing. Furthermore, our preliminary results show that the steady-state filtering implementation is critical for real-time processing of high sampling-rate neural signals such as wideband multiunit activity. This far more efficient neural decoding approach will enable the practical implementation of future large-dimensional, multi-signal and wireless neural interface systems.

# ENCODING AND DECODING STIMULI USING A BIOLOGICALLY REALISTIC MODEL: THE NON-DETERMINISM IN SPIKE TIMINGS SEEN AS A DITHER SIGNAL

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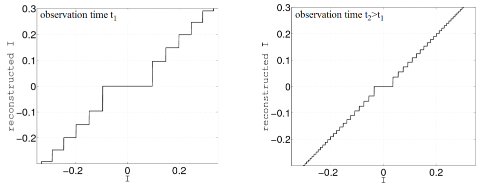
The mammalians retina conveys information by means of spike trains. Though, understanding the way these spike trains represent the stimuli is still a challenging issue, especially when considering their non-determinism. Interestingly, the spike-based code of the retina is binary-like, and thus we considered its study in a signal coding fashion. To do so, we specified a coding scheme based on the mean firing rate of spikes simulated by a realistic model of the mammalians retina. We, then, inverted the generated code to reconstruct the original input. Besides, we established some links between the processing occurring in the retina and state-of-the art methods in pure image coding. Finally, we gave a biologically plausible interpretation for the non-determinism in the spike firing timings.

We based our work on the biologically realistic model of the retina introduced in [1]. This model consists in a succession of linear filters, with added nonlinearities and a novel contrast gain control model. The spike-based code generated was compared to actual neural recordings and proved to be consistent with reality. Here we focus on the three deepest retina layers of the model: bipolar, amacrine, and ganglion cells layers. We restricted this study to the time course of the filters involved, so that no spatial filtering is taken into account.

We found that the behavior of the quantizer that we specified is similar to an analog-to-digital converter with a companding stage, i.e., involving a non-linear rectification before applying a uniform quantizer with a dead zone (see below, left figure). Though, two major differences are to be mentioned. First, the bioinspired model quantizers emphasizes high magnitude signals, while classical approaches aim at refining with more accuracy low magnitudes, which are more probable (Lloyd-Max quantizer). Second, the time dimension has been introduced in the quantization mechanism. This yielded an original coding/ decoding system which evolves dynamically from coarse to fine, and from uniform to non-uniform.

We interpreted the non-determinism observed in the spike firing timings as the addition of a random dither signal to the input stimuli. The dithering consists in perturbing the stimuli by a random signal $\nu$, with $\nu$ having a specific probability distribution function [2]. Here, we identified the behavior of the retina to a non-subtractive dithered quantizer. The coding/decoding system, that we propose, offers several interesting features as (i) the time scalability as well as (ii) the reconstruction error $\epsilon$ whitening and (iii) the de-correlation of $\epsilon$ from the input stimuli. The results observed are remarkable in terms of reconstruction quality (see below, right figure).



Input signal/reconstructed signal characteristic:
Behavior evolution of the bioinspired model.

Reconstruction quality with a non-dithered (left) and
a dithered (right) bioinspired quantizer.

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# HOW GOOD IS GRID CODING VERSUS PLACE CODING FOR NAVIGATION USING NOISY, SPIKING NEURONS?

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Our understanding of how the brain encodes navigation through space underwent a revolution with the discovery of grid cells in the medial entorhinal cortex (MEC) of rodents [4]. A grid cell builds a hexagonal lattice representation of physical space, such that the cell fires whenever the animal is close to a lattice point. In contrast, place cells in the hippocampus fire only at a single region. At the level of a single neuron, the multiple firing fields of a grid cell lead to an inherent ambiguity in the position estimate. Hence, for both codes precise information about position can only be gained from a population of cells.

We will present two different interpretations of the grid population code: the interval nesting hypothesis and the modular arithmetic hypothesis, similar to a concept first proposed in the context of the MEC by Fiete *et. al.* [3]. Interval nesting subdivides space with high resolution in a topographic and robust manner. The drawback is that the spatial range encoded is on the order of the longest spatial period. Modular arithmetic, on the other hand, can cover a much larger spatial range, which, in the best case, is given by multiplying all individual spatial periods together. Yet modular arithmetic is not robust to errors, which can affect both the spatial resolution and the spatial range covered. For these two hypotheses, we investigate the spatial resolution of the place code and the grid code, on a limited space with a finite amount of cells and families of tuning curves. For this purpose, we build a stochastic population coding model as in Bethge [1]. We assume that both codes should enable real-time readout of the rat's position while it is moving. For this reason, we have to consider short decoding times. Hence, since Fisher information methods fail to estimate the mean error in such cases [1], we apply Monte Carlo integration methods. To compare the two coding schemes, we calculate the minimum mean square error estimate and compute the expected error between the estimate and the true position.

Under the condition of noisy, spiking neurons, we demonstrate that the grid code, if it is organized as in the interval nesting hypothesis, outperforms the place code for any tuning width. However, if the modular arithmetic hypothesis holds, *i.e.*, the spatial periods are far shorter than the length of space encoded, the grid code has a higher distortion than the best place codes. This suggests that the MEC may provide a robust, local co-ordinate map over distances up to the maximum grid scale.

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# PRIMARY VISUAL CORTEX ENCODES COMPLEMENTARY INFORMATION ABOUT NATURALISTIC MOVIES AT DIFFERENT TEMPORAL SCALES

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Natural stimuli modulate the activity of visual cortex on a variety of temporal scales, yet it is still unclear whether visual cortical neurons employ more than one response time scale to encode such stimuli. We investigated this issue by analyzing the activity of neurons recorded in primary visual cortex (V1) of anesthetized macaques during binocular presentation of naturalistic color movies, and we used information theory to quantify the amount of information carried by neural codes operating at different temporal scales.

We divided the recording time into stimulus windows of 40–80 ms, and we computed the information carried by the neural response in each window about which stimulus window was being shown. First we measured the information carried by the spike count, simply quantified by the total number of spikes in the stimulus window. Then we measured the information carried by the temporal pattern of spikes, the latter being computed by subdividing each stimulus window into smaller time bins of size $\Delta t$ and converting the spike train into a sequence of 0s and 1s denoting the absence/presence of spikes inside each bin [1]. When considering temporal patterns of spikes with a temporal resolution $\Delta t$ of 8 or 16 ms, the information about which part of the movie was being shown conveyed by temporal spike patterns was up to 15% more than that conveyed by the spike count. This information gain did not increase further when considering resolutions finer than 8 ms, indicating that spike patterns carry information with a resolution of 8–16 ms or coarser. A previous study [2] showed that V1 neurons encode information also with respect to the phase of low frequency (1–4 Hz range) Local Field Potential (LFP) fluctuations. We investigated whether spike patterns carried information complementary to that carried by the phase of firing by quantifying if the joint knowledge of the precise spike pattern and the LFP phase of firing carried more information than either code considered alone. We found that this was the case: The information about the scene of the movie being shown gained by the simultaneous knowledge of the phase of low frequency LFPs and of the spike patterns occurred [3] was 50% higher than the information carried by spike patterns alone and 15 % higher than the information carried by the phase of firing alone. This suggests that the information carried by slow LFP fluctuations complements that carried by spike patterns.

In summary, we found evidence for multiple and complementary response time scales for the encoding of naturalistic stimuli in visual cortex. Informative codes range from spike timing precision at 10ms resolution to the much coarser phase of firing with respect to low frequency (few Hz) fluctuations. These findings suggest that, as hypothesized e.g. in [3,4], sensory cortices may enhance their information capacity by multiplexing complementary information at different time scales.

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# DECODING OBJECT CATEGORIES FROM EEG SIGNALS ON SINGLE TRIALS

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Object categorization is a fundamental task of perception and a basis of conceptual knowledge. In a series of experiments, we have measured the EEG signal of participants as they viewed visual images of animals, tools and other categories. A machine learning algorithm (Dalponte et al., 2007; Murphy et al., 2008, 2009) is then trained to identify the most informative time interval and frequency band within recorded EEG signals to decode the categorical class of the stimuli being processed.

Here we present two applications of this approach. In the first study, participants silently named a series of images of mammals and work tools. Single-trial prediction of category was highly accurate (mean 72%; range 57% to 80%) in the window 100-350ms and 4-18Hz. A regression analysis confirmed that categorical membership was the driving factor for the algorithm, rather than visual, lexical or semantic nuisance variables. The analysis was extended to use a sliding 100ms time-window in order to measure how the information used in making the category distinction becomes available over time. For a subset of the participants, whose data resulted in higher predictive accuracies, the most informative windows were as early as 70-170ms.

In a second study, we used continuous flash suppression (CFS: Tsuchiya & Koch, 2005) along with the aforementioned EEG data analysis to determine the earliest time point at which conscious and unconscious stimuli differ. We used CFS allows us to compare EEG signals in the visible condition (in which objects were consciously perceived) and the invisible condition in which participants were unaware of the presence or identity of the suppressed stimulus. While the machine learning algorithm remained highly accurate in predicting object category in the visible condition, performance fell to chance in the unseen condition.

Overall, these results provide further evidence that categorization occurs early in visual processing (Van Rullen & Thorpe, 2001) and that this early, perhaps initial and approximate, categorization plays a role in later semantic processing and in conscious awareness.

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# SYNCHRONIZATION BETWEEN MOTOR CORTEX AND MUSCLE DURING LOW-LEVEL FORCES: HIGH-RESOLUTION EEG STUDIES

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The synchronization between cortical motor areas and muscles was shown for the first time in monkeys (Murthy and Fetz, 1992; 1996) and three years later in humans (Conway, *et al.*, 1995). Using one channel MEG, Conway, *et al.* (1995) have recorded the activity over the contralateral motor cortex and muscles during maintained motor contraction. Applying coherence analysis they have shown synchronization between MEG and EMG in the beta-frequency range. For the last 17 years this beta-range corticomuscular coherence (CMC) has been investigated on a large scale and was shown that it is task-dependent, that it reflects attention, training, task compliance, displacement, and adjustment of the length-tension ratio. However, the functional significance of the beta-range CMC remained unclear. Therefore, we hypothesized that, if the beta-range CMC has a functional role it should correlate with the behavioral performance, such as the errors between target and exerted force. In Kristeva, *et al.* (2006) we in fact revealed such a correlation. This suggested that beta-range CMC may promote effective corticospinal interaction during steady-state motor tasks.

But how are motor cortex and muscles synchronized during isometric compensation of periodically modulated dynamic forces? We investigated this at 4% MVC and showed that the corticomuscular network oscillates at gamma frequencies during predictable dynamic forces to yield rapid integration of visual, proprioceptive and cognitive information (Omlor, *et al.*, 2006). In Chakarov, *et al.* (2009) we showed that beta-range CMC accompanies not only static low-level forces and that the sensorimotor system may resort to stronger and also broader beta-range CMC to generate stable corticospinal interaction during increased force level (from 8 to 16 and 24% MVC), as well as when compensating for dynamic modulated forces. We investigated the CMC at 8% MVC in 13 subjects in more detail and found that the corticospinal interaction during static forces is in 11 out of 13 subjects in beta- and in two subjects in alpha-range. During dynamic force there was a shift of the frequency of the CMC mostly towards low gamma-range.

Ongoing research in the laboratory shows stronger CMC with unpredictable forces than with predictable ones.

The results show that similar to the cognitive systems (Tallon-Baudry, 2009) as well as in the motor system there is no one-to-one relationship between frequency band and function. Further, the corticomuscular coherence is a reliable readout of the current state of the corticomuscular network during low-level forces.

# AN ONLINE BRAIN-MACHINE INTERFACE USING DECODING OF MOVEMENT DIRECTION FROM THE HUMAN ELECTROCORTICOGRAM

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Brain-machine interfaces (BMIs) can be characterized by the approach used to translate brain signals into effector movements. Here we use a “direct motor” BMI approach where movements of an artificial effector (e.g. movement of an arm prosthesis to the right) are controlled by motor cortical signals that control the equivalent movements of the corresponding body part (e.g. arm movement to the right). This approach has been successfully applied in monkeys and humans by accurately extracting parameters of movements from the spiking activity of multiple single-units. Here we show that the same approach can be realized using brain activity measured directly at the surface of the human cortex (electrocorticogram, ECoG).

Three subjects suffering from intractable pharmaco-resistant epilepsy voluntarily participated in the study after having given their informed consent (study approved by the Freiburg University Hospital's Ethics Committee). As a part of pre-surgical diagnosis all subjects had 8x8 ECoG grid implants (4 mm electrode diameter, 10 mm inter-electrode distance, Ad-Tech Medical Instruments, USA) over the hand and arm motor cortex. Subjects interacted with an experimental paradigm shown on a computer screen. Each trial consisted of a pause phase (1-2 sec) followed by a preparatory informative cue (1-2 sec) which informed the subject to prepare for executing or imagining a hand/arm movement to the left or to the right using the hand contralateral to the implantation site. After a delay of 2-3 sec, a go cue was presented and subjects had to perform the movement execution or imagination within the next two seconds. Subsequently, a cursor on the screen was moved according to the movement direction decoded from the subjects’ ECoG signals.

Closed loop BMI control of movement direction was realized using low-pass filtered (symmetric Savitzky-Golay filter, 2nd order, between 0.25 and 1 sec window length) ECoG signals during movement execution or movement imagination. For movement execution significant BMI control was achieved for all three subjects in all 7 sessions with correct directional decoding in 69%-86% of the trials (79% on average across all sessions). Movement imagination was carried out with only one subject where 3 out of 4 sessions showed significant BMI control with correct decoding in 66%-72% of the trials (69% on average).

In summary, our results demonstrate the principle feasibility of an online direct motor BMI using ECoG signals. Thus, for a direct motor BMI, ECoG might be used in conjunction or as an alternative to the intra-cortical neural signals, with possible advantages due to reduced invasiveness.

Acknowledgements

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# TEMPORAL PATTERNS OF NEURAL ACTIVITY IN RAT SOMATOSENSORY CORTEX CORRELATE WITH TRIAL-TO-TRIAL PERCEPTUAL JUDGEMENTS IN A TWO TEXTURE DISCRIMINATION TASK

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The temporal precision at which neural responses carry information has been systematically investigated over the last 20 years in several sensory structures. Substantial evidence (reviewed in [1]) shows that the timing of spikes registered with millisecond precision carries significantly more information than that carried by spike counts over windows of tens or hundreds of milliseconds. However, it is not yet known whether the information advantage of spike timing codes over spike counts is used by the brain to control behaviour.

To investigate the relationship between the timing of neural responses and behaviour, we considered spike trains recorded from small neural clusters in rat barrel cortex while the animals performed a discrimination between two surfaces, one rough and one smooth, that they could only explore by whisking [2]. The rat was required to turn in opposite directions for a reward according to the contacted texture. Our strategy was to compare the information carried by spike times and spike counts in correct and in wrong trials. We reasoned that if a neural code is used to produce correct behaviour, it should contain less information in trials leading to wrong behaviour.

We compared the per-trial mutual information about texture carried by spike counts and times in a window of duration T (a free parameter) starting at the time of first contact of the neural cluster's principal whisker with the texture. The information in spike counts was computed using Shannon's mutual information formula and limited sampling bias corrections [1]. The information in spike times was computed through a similar procedure, with an additional response compression algorithm, based on Principal Component Analysis of the temporal response profile, and inspired by Optican [3] but refined to increase limited sampling robustness and ensure full fairness in comparing information in wrong and correct trials.

We first investigated the information content of neural codes during correct trials and found that there was significantly more information in spike times than in spike counts. At $T = 30$ ms (the time window with peak information for both codes) across the population (mean ± SE) spike counts carried $0.05 \pm 0.03$ bits of information. while spike times carried about 80% more, $0.09 \pm 0.03$ bits. We then investigated whether the inclusion of error trials decreased spike timing information more than it decreased spike count information. We found that inserting error trials significantly decreased ($p<0.05$, paired *t*-test) spike timing information, but did not significantly decrease information in spike counts from first whisker contact.

Taken together, these results suggest that when considering responses of neurons in rat barrel cortex from the time of first whisker contact with an object, spike times carry more information and influence trial to trial behaviour more significantly than spike counts do.

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# REDUCTION OF CORRELATED NOISE IN THE MACAQUE PREFRONTAL CORTEX DURING CONSCIOUS VISUAL PERCEPTION

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The cortical mechanisms mediating visual awareness are thought to exploit a large population of similarly tuned neurons explicitly representing a perceptually dominant visual pattern through changes in its mean firing rate. However, inherent limitations of population rate coding schemes such as noise detected in the correlated response variability across neurons could constrict the encoding power of such a cortical network and thus decrease the probability of this encoding strategy. Studying the differences in the noise correlation structure of a tuned population between purely sensory visual stimulation subjective visual perception could thus provide fundamental insights into the mechanisms of conscious visual perception. Here we show that in the macaque prefrontal cortex perceptual dominance under conditions of visual rivalry is accompanied by decorrelated discharges across neurons sensory tuned to the dominant stimulus, compared to their significantly correlated fluctuations when the same stimulus is perceived without competition. We propose that noise decorrelation in prefrontal cortical circuits is optimal for achieving perceptual dominance during visual awareness by substantially improving the encoding accuracy of the dominant neuronal ensemble. Our findings also provide the first electrophysiological demonstration of the contribution of prefrontal cortex to visual consciousness, a hypothesis previously suggested by theoretical models as well as human functional imaging studies.

# MICROCIRCUITS IN THE PREFRONTAL CORTEX: *IN SILICO* INVESTIGATION OF THEIR ROLE IN THE EMERGENCE, MAINTENANCE AND TERMINATION OF PERSISTENT ACTIVITY

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Working memory, namely the ‘on-line’ monitoring or manipulation of information, is the basic neural process involved in shaping behaviour over time. A classical procedure used to evaluate working memory is the delayed match to sample task. *In vivo* recordings have shown that, during the delay period, neurons in the prefrontal cortex (PFC) sustain their activity, presumably in order to hold information about the cue, the subsequent execution of the action or the anticipation of reward.

The ability of prefrontal neurons to display persistent activity, characterized by robustness to noise or distracting stimuli, has been intensively investigated with the use of abstract or conductance-based large-scale model networks of point neurons. According to these computational studies, synaptic reverberation is essential for the emergence of sustained activity, while a slow excitatory current (iNMDA) is necessary for its stability and robustness to distractors.

A main drawback of these models is their dependence on homogeneity in terms of biophysical mechanisms and synaptic connections as well as the need for unrealistic fine tuning of synaptic connections, which is in contrast with existing anatomical and electrophysiological data. Moreover, experimental evidence indicates that in addition to synaptic mechanisms, a somatic current that underlies a delayed afterdepolarization (dADP) can also support regenerative events in single layer V prefrontal pyramidal neurons.

In an effort to bridge together the abstract recurrent circuit models with the biophysical heterogeneity of individual neurons, we undertook a bottom-up approach and constructed an *in silico* model of a layer V PFC microcolumn with the aim to investigate the role of different synaptic and cellular biophysical mechanisms in persistent activity. All neuron models (4 pyramidal and 1 interneuron) were simulated in the NEURON simulation environment and included modeling equations for the various types of ionic mechanisms, known to be present in these cells. Both the density and distribution of these mechanisms as well as specific connectivity properties (location, number, delays) within the network were validated against experimental data.

This biophysical model network was robust to connectivity modifications and corroborated previous theoretical findings regarding the critical role of the NMDA current in generating persistent activity. Furthermore, we identified the slow inhibitory current ($iGABA_B$) as a new mechanism that serves as a gate for persistent activity induction and feed-forward inhibition, but not excitation, as a mechanism for termination. Finally, we showed that the delayed afterdepolarization mechanism (dADP) modulates the firing properties as well as the stability of the sustained activity. In summary, based on a detailed, heavily validated, biophysical microcircuit model, our work provides a theoretical dissection of the role of synaptic (iNMDA and $iGABA_B$) and intrinsic (dADP) mechanisms in modulating different aspects of persistent activity in the PFC.

# FUNCTIONAL ARCHITECTURES: CODING FOR STRUCTURED FLOWS ON MANIFOLDS EMBEDDED IN A HIERARCHY OF TIME SCALES

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Research on bridging the gap between neural system's structure and function on the one hand, and behavior on the other one, has been dominated so far by information processing approaches. Such approaches, contributed important results in their effort to discover the coding scheme that allows the neural system to code and process information, while they also brought forward the controversy between firing rate and spike timing based principles of neural coding. However, there is yet no general agreement on how the function of the neural system contributes to the organization of behavior.

Recently alternative approaches have been proposed that view the brain us a system far from equilibrium in which lower dimensional patterns emerge as a result of the tendencies of the brain regions to segregate and integrate based on functional requirements.

In this context, we built on a novel hypothesis stating that the neural system codes for Structured Flows on Manifolds (SFMs). SFMs have been recently proposed as a general framework for linking the high dimensional neural dynamics with the inherently low dimensional functional dynamics of basic human behaviors. They are defined as deterministic mathematical representations capturing the fast adiabatic collapse of an originally high dimensional phase (state) space (such as the one spanned by the relative neural observable variables) onto a low dimensional subspace, the manifold, followed by functionally relevant dynamics on a slower time scale, the phase flow. Evidence supporting such an hypothesis can be found in recent and ongoing experimental research on the neural correlates of sensorimotor and bi-manual coordination as well as of simple discrete and rhythmic movements. The methodology of the above mentioned experiments focuses on the search for a topological isomorphism between low dimensional patterns of neural spatiotemporal dynamics and behavioral dynamics.

In the present work we show how SFMs' framework can be extended to account for complex human behavior. We postulate that the neural system codes for a set of SFMs that constitute the humans' dynamical and functional repertoire. AA secondary mechanism operating on a slower time scale and based on pattern competition plastically activates the SFMs to compose more complex functions. The slow and fast subsystems define a functional architecture allowing for a novel modeling approach of behavioral organization.

The underlying hypothesis that complex behaviors can be decomposed in simpler building blocks (or movement primitives) is well established in the motor control literature. Simulations of generating cursive handwriting are provided as proof of concept.

# DYNAMICAL EMERGENCE OF A NEURAL SOLUTION FOR MOTION INTEGRATION

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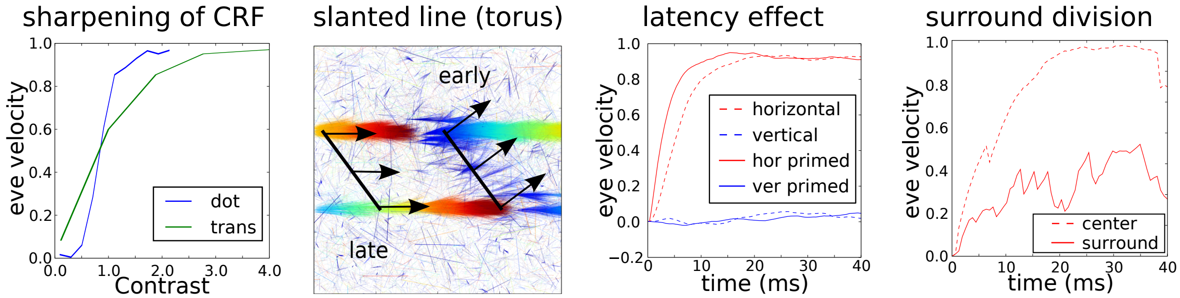
A central challenge in neuroscience is to explain how local information as processed by single neurons is integrated to give a coherent global response at population level. An illustration of this problem is the early stages of the visual system. Local motion is processed in area V1 by neurons having only access to a limited portion of the visual field, their receptive field. As a consequence, information is often incomplete and sometimes ambiguous. One well-known example is the aperture problem: when a single elongated line crosses the receptive field, it is only possible to extract the component of the speed perpendicular to its orientation. Since there is only one 1D edge, geometrical rules working at more global levels such as the Intersection-Of-Constraints rule fails. Still there are many experimental evidence that populations of higher-stage neurons, such as MT cells, can solve this aperture problem and dynamically reconstruct the 2D motion of this simple object.

Here, we explore a more parsimonious solution where these 2D motion analyzers could be understood as a product of velocity prediction. In natural scenes, translation of visual objects are highly predictable thanks to their physical properties (rigidity and inertia). We implemented this in a motion field: in a retinotopic velocity map, predictions are propagated by lateral recurrent interactions inferring that each velocity vector is approximately conserved along path-lines. In the framework of a probabilistic representation, the filtering and smoothing equations involve integrals over the hidden variables and define a dynamical Markov random motion field. A dynamical solution was approximated using Sequential Monte Carlo methods (also known as "particle filters"). We tested our model against a wide range of motion stimuli, going from random dot patterns or line-drawing objects to moving plaids and textures.



Although no explicit mechanisms of 2D motion was introduced, the predictive coding constraint was sufficient to let several features of 2D motion detectors emerge from the dynamics of the probabilistic motion field. We observed that the system exhibits a non-linear binary response when tracking one or a few dots compared to the smooth response of the first-order system: As predicted by a mean-field model of the system, a dot is either tracked or lost. The algorithm exhibits several properties observed in low-level motion perception, such as sharpening of the contrast response function for a dot compared to a grating, activation along the line-endings of the moving slanted line, an advance in response latency when information was cued, or center-surround suppression (see respectively in Figure from left to right). This is consistent with neural models where interactions are heuristically tuned and may contribute to a functional approach in our understanding of low-level visual system.

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# NEURONAL POPULATION CODING IN VERTEBRATE CPG: A MULTI-UNIT STUDY DURING FUNCTIONAL MOTOR ACTIVITY

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Central pattern generators (CPG) are neuronal ensembles underlying standard movements such as walking, swimming, and scratching. Often these standard movements can be initiated and sustained without cortical input indicating that CPG's reside locally in the spinal cord where they constitute the neuronal basis for programmed motor tasks.

The operating principles for CPG's in the spinal cord are unresolved. Basic properties such as the number of neurons participating and their connectivity are unknown. In the turtle, intrinsic properties of the individual cells are of minor relevance for the collective behavior of the neuronal ensemble during a motor task (Berg et al., 2008). Therefore the aim of the present study is to investigate neurons at the population level during functional activity in order to obtain further knowledge about the architecture of CPG's.

We use extra-cellular multi-electrode recordings in the spinal cord of the turtle to obtain information about an ensemble of neurons during a scratch reflex. The preparation constitutes a well defined system with controlled input and measurable output to monitor functional activity of the spinal column.

We find that isolated units are rhythmically participating with different but constant phase lag in the cycle motor pattern as previously observed (Berkowitz, 2002). Our method allows us to investigate the distribution of firing rate across the population of units participating in the neural ensemble and the spike count correlations between different neurons. With these studies we hope to elucidate some of the basic principles of functional neuronal activity in an adult vertebrate.

# STATISTICS OF CORTICAL UP AND DOWN STATES DURING SLEEP

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Even in the absence of sensory stimulation (*e.g.*, during sleep) the cortex shows complex spontaneous activity patterns, which have been suggested to reflect an ‘‘off-line’’ mode of information processing [1,2]. During sleep and quiet wakefulness, cortical spontaneous activity is dominated by ‘‘slow oscillations,’’ consisting of alternating ‘‘DOWN’’ states of generalized neural silence and ‘‘UP’’ states of massive, persistent network activity. Here we analyzed data from D. Euston, M. Tatsuno and B. McNaughton, consisting of massive parallel recordings of neural spiking activity from medial pre-frontal cortex (mPFC) of a rat during sleep [3]. The rat was implanted with microdrives containing 12 tetrodes, allowing simultaneous recording of 116 neurons from the anterior cingulate and prelimbic cortices.

We characterized the statistics of UP and DOWN states using a Hidden Markov Model (HMM) (fig1A-B). First, we found that the distribution of UP state durations is much more irregular than the distribution of DOWN durations, consistent with recent findings indicating that UP state durations are random [4]. These differences can be understood if we assume that the DOWN state is dominated by the dynamics of ionic currents whereas the activity in the UP states is maintained by the recurrent excitation in the network. Second, we found that a subset of neurons fires at the start of the UP states in an ordered way (fig1C), as found in auditory cortex [1]. The same phenomenon was found towards the end of the UP states (fig1D). Third, the initiation of the UP states contains two patterns of rate configuration in the population of neurons. Finally, we concentrated on precise spike coincidences across the neurons and characterized them by the distribution of their complexities, i.e. the number of synchronous neurons. The HMM identified different states of synchronous spiking activity by different distributions of complexities. Comparison of empirical distributions to the ones predicted by the firing rates [5] revealed the occurrence of excess of synchronous spike events.

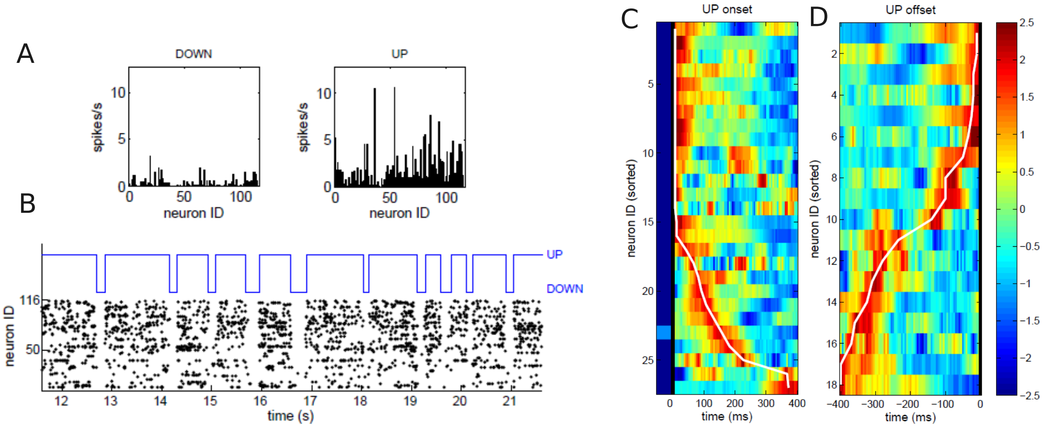

**Fig1**. Detection of UP and DOWN using a HMM. **A**: the model recognized one state of low general activity and one state of high general activity. **B**: the spiketrains of the 116 neurons in a piece of data of 10s are shown together with the sequence of states identified by the HMM (blue trace). **C-D**: The Z-scores of the firing rates of a selected subset of the neurons are represented in color code and ordered according to their activation time (white line). The activity was aligned to the UP state onset/offset (C/D).

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# DECODING BIRDSONG FROM AUDITORY MIDBRAIN NEURONS

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Understanding the neural mechanisms underlying auditory perception remains a fundamental goal in auditory physiology. In the Zebra Finch (ZB), much progress has been made understanding the mechanisms by which single neurons encode complex sounds. ZB midbrain neurons show spike rates correlated with spectro-temporal modulations of natural and synthetic sound [1], suggesting these neurons are important for recognition. However, little is known about how populations of these neurons are involved in song perception.

Recent work in the auditory cortex of ferret [3] studied this question using the optimal linear estimator to reconstruct spectrograms. We address this issue in songbird by reconstructing spectrograms using a nonlinear, Bayesian model of ZB midbrain neurons. We model spike trains as point processes with instantaneous firing rates given by a generalized linear model (GLM) that takes song spectrograms as input. The linear stimulus filtering properties of the model are incorporated via a spectro-temporal receptive field (STRF) and history-dependent spike effects are incorporated with a spike-history filter. We then calculate *maximum a posteriori* (MAP) estimates of song spectrograms given spike trains from real ZB neurons (for a detailed discussion see [2]).

We study how MAP estimates depend on prior information used in reconstructions and on the stimulus filtering properties of midbrain neurons. Using a white-noise Gaussian prior, we find that neuronal responses can be used to roughly identify vocal onset periods from silent periods; however reconstructions don't capture fine spectro-temporal detail. Given prior knowledge of song spectro-temporal correlations we find close resemblance between MAP estimates and input spectrograms (Fig. 1).

Our reconstructions suggest that song recognition can arise by combining spike trains from auditory midbrain neurons with prior knowledge of the statistics of birdsong power distributions. Importantly, our method allows us to study reconstruction accuracy as a function of this prior knowledge.

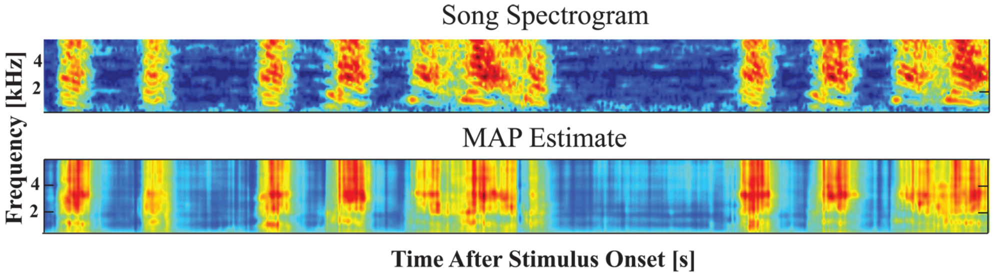

Figure 1: Population decoding of a spectrogram using GLM STRFs and real spikes

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# HETEROGENEITY IN RESPONSES OF NEIGHBORING NEURONS IN CAT PRIMARY VISUAL CORTEX

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The model of cortical organization into radial columns suggests that the response characteristics of adjacent neurons in cortex are very similar. Optical imaging studies and successive recordings of single neurons parallel to the cortical surface show a continuous variation of tuning preferences to stimulus parameters like orientation or spatial frequency on a macroscopic level of a few 100 micrometers. To understand the coding principals of neuronal populations it is, however, necessary to quantify the degree of similarity between the responses of the single neurons that are part of one such population.

In this study we set out to determine this degree of similarity by recording simultaneously from 2 to 4 neurons with a single high impedance sharp pipette, which gave spikes that were easily separated by amplitude alone. The recordings were made in the primary visual cortex of anesthetized cats. We compared the responses of the neurons to visual stimulation with drifting sine wave gratings of varying orientations and spatial and temporal frequencies, white noise stimuli, and ‘natural’ scenes from movies. Based on average spike counts, neighboring neurons had very similar orientation preferences, but had very different preferences for other stimuli — as much as between randomly sampled neurons in some cases. The fine temporal structures of the spike discharge of neighboring neurons were quite dissimilar. The strengths of the correlations in spike timing were not limited by the response variability of the individual neurons, nor did the different stimuli elicit corresponding differences in correlation strengths between adjacent neurons. The strength of the spike time correlations were best predicted by the similarity of the tuning characteristics between neighboring neurons in response to drifting gratings, but the grating responses were poor predictors of the correlation strength in responses to the movie scenes. These results show that within the functional continuum suggested by cortical maps and functional columns there is a yet unexplained individuality in the spiking output of neighboring neurons in response to the same stimulus.

## Acknowledgment

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# A PARAMETRIC STUDY OF INFORMATION TRANSFER BETWEEN STIMULATING AND RECORDING ELECTRODES IN A CLOSED LOOP BRAIN MACHINE INTERFACE

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One of the most challenging goals in neuroscience is to elicit natural sensations with electrical microstimulation. This is a fundamental step toward providing feedback in a bidirectional Brain Machine Interface where recorded neural signals drive an external device and intracortical microstimulation (ICMS) provides information about the interaction with the environment.

We studied this issue in anaesthetized rats implanted with an array of 16 stimulating electrodes in the barrel cortex and an array of 16 recording electrodes in the vibrissal representation of motor cortex. In order to maximize the amount of mutual information [1] between the stimulation pattern and the recorded population activity, we explored the stimulation parameters for the stimulating electrodes and the decoding parameters for interpreting the evoked spiking activity in the recording electrodes. We found that maximal amounts of information were extracted when binning the recorded neural activity within the first 500 ms post-stimulation with a fine temporal precision, usually in the order of 5-10 ms, using stimulation trains with amplitude of 80-150 µA and pulse frequency of 200-500 Hz.

To understand whether such information could be effectively used to drive a closed loop neural interface, we set up an experiment in which fine-precision spiking activity recorded from motor cortex is used to drive the movement of a simulated point mass within an predefined elastic force field, acting like a viscous fluid, and its actual position is encoded as ICMS delivered on barrel cortex [2]. In order to translate an N-dimensional response into a force vector and to convert the position of the point mass into a pattern of stimuli we used a dimensionality reduction algorithm based on Principal Component Analysis. We found that the algorithm was robust to noise in the recorded dataset but was highly dependent on stimulation and recording parameters.

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# A REAL-TIME BRAIN-MACHINE INTERFACE COMBINING PLAN AND PERI-MOVEMENT ACTIVITIES

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Brain-machine interfaces (BMI) map relevant neural activities to the intended movement, known as ‘decoding’. Information about various states of a movement are encoded in the motor areas. These include the kinematic states such as velocity and higher level states such as the intended target. Real-time BMIs have mostly focused on decoding individually either the goal of a movement or its kinematics. However, for goal-directed movements, target information can greatly improve the kinematics decoding.

We consider real-time decoding of goal-directed movements with *unknown* duration. We develop a recursive Bayesian decoder that takes advantage of the goal information to reduce the root mean-square (RMS) error in movement trajectory reconstruction. Our decoder has two major components. The first component builds a new state-space model for the kinematics by exploiting the optimal feedback control model of the sensorimotor system. This contrasts with prior work that has used smoothed random-walk (RW) or open-loop controlled models . Any goal-directed model inherently depends on the movement duration not known a priori to the external observer of the neural signal. To be practical, the second component of our decoder addresses this timing uncertainty in contrast to other work that assumes it is known. This is done by exploiting a bank of parallel point-process filters (P-PPF) that calculate not only causal estimates of the state at each time based on the neural activity, but also the likelihood of the movement duration based on this activity. The overall decoder is a feedback-controlled P-PPF (FC-P-PPF).

We first tested our decoder on the simulated neural spiking activity of 20 neurons generated in response to 55 actual reaching movements of 150–400 ms duration performed by a rhesus monkey. This activity was simulated using the velocity tuning model. We found that FC-P-PPF reduced the RMS error in trajectory reconstruction from that of the RW point-process filter by 40%.

We then implemented a real-time BMI exploiting FC-P-PPF in an instructed-delay center-out task with 4 targets performed by a monkey. Multi-electrode spiking activity was recorded from the dorsal premotor cortex (PMd) and supplementary motor area (SMA) from which 19–20 cells were isolated. Our real-time BMI had two phases and combined *two* algorithms: (1) During the instructed delay, a maximum-likelihood decoder was used to decode the upcoming target from the plan ensemble spiking activity modeled as a point-process for each neuron. (2) After the delay period, the BMI transitioned into the kinematics decoding phase, exploiting the decoded target in FC-P-PPF. The peri-movement ensemble spiking activity in this phase was modeled and fit as a point-process tuned to velocity and position for each neuron. The estimated cursor position was displayed on the screen in real-time.

We measured performance as the percentage of trials with the target correctly acquired. For this monkey, the performance was 73%–85% with an average of 77% across multiple sessions using only 19–20 cells. The average correct acquisition time was about 1 s. From our real-time experimental results we conclude that properly combining plan and peri-movement activities improves the performance of BMIs.

# SPIKE LATENCY CODING OF ORIENTATION IN THE PRIMARY VISUAL CORTEX

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Accumulating evidence from behavioral experiments and imaging studies shows we are able to discriminate between different visual objects at a remarkable speed. The high computation speed yields a strong constraint on the code used to relay signals between cortical areas.

Conventional neural coding research has ignored the temporal structure of the neural response and focused, in many cases, on the neural mean response over long timescales that are often beyond the relevant behavioral timescale. It has been suggested that the temporal structure of the neural initial response and in particular response latency are used by the central nervous system for fast communication of information between different brain regions. However, the accuracy of such a scheme has not been analyzed rigorously.

Here we addressed this question in the framework of orientation coding by primary visual (V1) cortical cells of the monkey. To this end, simultaneous recordings of multiple V1 neurons over many repetitions per each orientation were performed. The spike data from these recordings were used to investigate the utility of first spike latency for encoding information about the orientation of visual stimuli.  Cells in V1 are known to code for the orientation of a grating stimulus by their rate of firing. Typically, V1 cells show a maximum firing rate in response to a 'preferred orientation'. We find that many cells in the monkey V1 also show tuning of their first spike time latency to the orientation of the stimulus. Most cells have the shortest latency at the preferred orientation of their rate tuning curve.

Using various statistical measures, we quantified the performance of a highly nonlinear readout mechanism, which determines the stimulus orientation by the preferred orientation of the cell with the shortest first spike latency, the temporal-Winner-Take-All (tWTA). In the context of a two-alternative forced-choice paradigm, we find that the tWTA discrimination accuracy is comparable to that of a conventional rate-code readout, which takes into account the total number of spikes fired by the cell in response to the visual stimulus. The accuracy of the tWTA readout can be further increased by considering a generalized n-tWTA readout, which determines the orientation using the preferred orientation of the cell or group of cells which fired the first n spikes. The n-tWTA readout helps in overcoming the interference from baseline firing. This study demonstrates that a readout based on the first few spikes fired may significantly improve response speed at a small cost to the accuracy of the decision.

# CATEGORICAL REPRESENTATION OF A HUMAN/MONKEY FACE CONTINUM IN THE HUMAN AND NON-HUMAN PRIMATE TEMPORAL LOBE

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Categorization of faces is fundamental for social interactions of primates. To understand its neural basis, we investigate how human and monkey face categories are represented in both the human and non-human primate brain. As stimuli, we use realistic three-dimensional morphed faces that linearly span the continuum between humans and monkeys (Fig. 1A). Extensive behavioral tests in both species revealed categorical perception with a shift of the categorical boundary towards the own species (Fig. 1B). This suggests that both species perceive the same stimulus continuum in a fundamentally different way. During a fixation task, we recorded from the temporal lobe extracellular signals in monkeys and BOLD signals in humans. To analyze the data, we used a multivariate pattern classifier approach based on Support Vector Machines and correlations. Consistent with the psychophysical results, we found an "own-species" bias in the categorical representation of human and monkey faces at the level of single neurons as well as in the population response in the inferior temporal lobe of the monkey. (Fig. 1C). Symmetrically, we found a categorical response with an own-species bias in the activation patterns of the left human STS. In addition, human ventral temporal cortex showed a higher sensitivity for human faces. Our results are the first to demonstrate the neural basis of categorical representation of a facial attribute in the primate brain. In addition, our data show that both psychophysical and neuronal data can show categorical boundary shifts indicative of the behavioral relevance of prototypical categories.

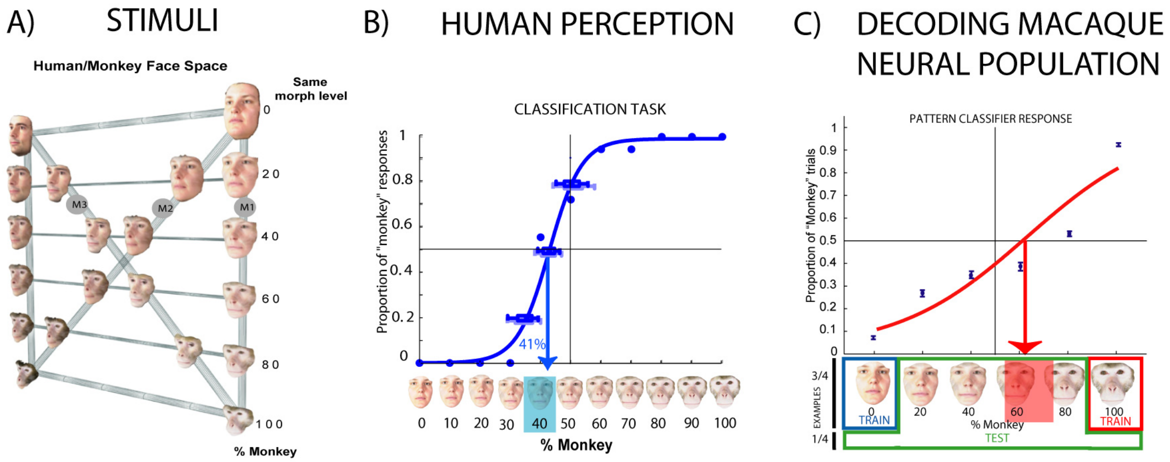

**Fig.1.** A) Face-space used as stimuli. B) Psychometric curve derived from human responses. C) Psychometric curve decoded from a population of neurons recorded from the inferior-temporal (IT) cortex of the macaque.

# A GRAPH THEORY APPROACH TO NEURONAL ENSEMBLE DECODES

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The ability to decode information from neural signals is a basic requirement for neural prosthetic systems. Many decode methods currently being used assume that neurons are independent. There is potentially a loss incurred when this assumption is made. We developed an algorithm that produces a functional map of conditional probability distributions to assess how the perceived function of a neuron changes when other simultaneously recorded neurons are considered. We recorded the activity of electrode arrays implanted in medial intraparietal sulcus (MIP) and dorsal premotor (PMd) cortex of non human primates performing a reaching task coupled with saccades, smooth pursuit and no eye movement. Our algorithm produced a connectivity map of the neurons that allowed us to investigate how much information is lost when a neuron is assumed to be independent. Two types of neurons emerged from the analysis. The tuning curve of some neurons was ill defined and shifted as a function of network activity. In contrast, other neurons had rigid tuning curves that were independent of the network. This result shows that an individual neuron's tuning curve is ill-defined and is only meaningful when considered from the point of view of the population. Many neurons where anchored to a single direction and shifted their peaks within a fixed range of directions. We developed decode algorithms based on this graphic theoretic framework. By including correlations, we increased the information decoded from the population by up to 20%, approaching 95% of the available information in some cases. We propose that networks in MIP and PMd are composed of neurons forming malleable networks anchored by neurons with static receptive fields.

# MULTISENSORY FEEDBACK IMPROVES THE PERFORMANCE OF A CORTICALLY-CONTROLLED BRAIN-MACHINE INTERFACE

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Current brain-machine interfaces (BMI) largely rely on visual feedback to guide cursor or robot movements, thereby neglecting other relevant sensory modalities. For instance, it is well known that patients suffering from the loss of proprioceptive sense exhibit considerable motor deficits. We describe a set of experiments designed to test two hypotheses: (1) the spiking activity in primary motor cortex (MI) carries more information about movement when multisensory feedback is available and (2) the inclusion of multisensory feedback (i.e. vision and proprioception) improves the movement of a cortically-driven cursor.

Two monkeys (Macaca mulatta) were trained to observe/move a visual cursor and hit a sequence of randomly placed targets while resting their arm in a two-link robotic exoskeleton. A chronically implanted, micro-electrode array composed of 100 electrodes was used to record the spiking activity of an ensemble of neurons in MI.

In the first experiment, the monkeys observed the replay of previously recorded target positions and cursor trajectories in three conditions. In the Visual Playback condition both the cursor and the target were visible during replay and the animal voluntarily maintained a static arm posture. In the Proprioceptive Playback condition both the cursor and target were invisible and the monkey's hand was moved through the replayed trajectory of the invisible cursor by the robotic exoskeleton. In the Visual+Proprioceptive Playback condition both the target and the cursor were visible and the monkey's hand was moved through the replayed cursor trajectories by the exoskeleton.

In the second experiment, the monkeys used a BMI to move a visual cursor in three separate experimental conditions. In the first condition, Visual BMI, the monkeys moved the cursor via the BMI while voluntarily maintaining a static arm posture in the robotic exoskeleton. Next, in the Visual and Proprioceptive BMI condition, the monkeys controlled the cursor via the BMI while their arm was driven by the exoskeleton through the decoded cursor trajectories, thereby providing the monkeys a veridical proprioceptive estimate of the cursor position. Lastly, we included a control condition, Visual and Noisy Proprioceptive BMI, in which the monkeys moved the cursor via the BMI while their arm was moved through a trajectory uncorrelated to the decoded trajectory of the visual cursor.

We demonstrate the benefit of adding additional feedback modalities in order to improve the control of a cursor driven by neural activity in MI. Mutual information and directional tuning analyses demonstrate that the presence of multisensory feedback (i.e. vision and proprioception) during observation of replayed movements evokes neural responses in MI that are almost indistinguishable from those responses measured during normal movement. Similarly, when vision and proprioception are congruent during decoding, the time to successfully complete the task decreased, and the cursor paths became straighter when compared with the incongruent feedback conditions. These findings provide the groundwork for augmenting the training and control paradigms of cortically-controlled BMIs with multiple forms of natural or surrogate sensory feedback.

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# LAMINAR AND TEMPORAL DISTRIBUTION OF STIMULUS INFORMATION IN LOCAL FIELD POTENTIALS

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Recent studies have reported that the phase of low-frequency (< 10 Hz) Local Field Potentials (LFPs) in primary sensory cortices carries stimulus related information and disambiguates the information about different stimuli evoking similar spike rates [1, 2]. Additionally, attentional modulation and cross-modal integration may be mediated by phase resetting of such slow LFPs [3, 4, 5]. Taken together, these empirical findings suggest a potential role of the phase of low-frequency network fluctuations in sensory processing. However, it yet unclear how these informative LFP phase values arise within the laminar organization of cortical columns. To address this issue, we performed current source density (CSD) recordings with multielectrode arrays in the primary auditory area of anaesthetized rats during the presentation of complex naturalistic sounds. Information analysis of CSD phases recorded across different laminae in such conditions revealed that the bulk of the LFP phase information originates at points tightly localized both in space and time. In fact, most of the LFP phase information was found to originate from CSD dipoles in the granular and superficial layers. These discrete “CSD events” occur in a reliable way mostly at precise times during the stimulus presentation and have a repeatable laminar and temporal structure. The same CSD events observed during stimulation occur also during spontaneous activity, suggesting that their occurrence correspond to activation of a stereotyped columnar computation. During both spontaneous and stimulus driven periods, CSD events occurred at rates in the delta range (ca. 1–4 Hz), and they generated LFP waveforms which contained a variable amount of beta and gamma power. Interestingly, the CSD events we identified appear to come in a limited number of discrete classes. Our findings point to an “event driven” mode of operation of sensory cortex in which the phase provides stimulus related information by indicating the time relative to stereotyped sensory driven columnar activations.

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# DECODING MOVEMENT DIRECTION FROM THE ACTIVITY OF MULTIPLE NEURONS IN THE HUMAN FRONTAL LOBE

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Decoding motion kinematics can be used both by brain-machine interfaces for controlling external devices and in developing a basic research understanding of how different brain areas encode and control movement. The vast majority of directional decoding studies focused on the primary motor cortex, where the firing rates of most neurons directly encode the trajectories of hand movements [Shoham et al. 2005], as compared to the more complex movement encoding observed in non-primary motor cortex (non-MI) datasets [Tankus *et al*. 2009].

In this study, we are applying various decoding strategies to multiple single-unit spike trains from several non-MI brain areas, such as the supplementary motor area (SMA proper and pre-SMA) and the cingulate cortex (both anterior (ACC) and posterior (PCC)) recorded from five patients with pharmacologically intractable epilepsy undergoing invasive monitoring with intracranial depth electrodes to identify the seizure focus for potential surgical treatment. Participants performed motor tasks including a center-out task (moving a computer cursor from a central location to 8 peripheral ones) and continuous movements in a maze game using a stylus pen and a joystick. Interestingly, we generally find that decoding is feasible despite the complexity of encoding seen in this dataset. For example, decoding movement direction in an 8-direction center-out task resulted in a classification accuracy of 67.2% in one of the patients, significantly above the chance level (chance level: 16%, $p < 0.005$, 69 units recorded simultaneously). We are currently developing more sophisticated decoding methods that will be optimized for extracting kinematic information from this type of data.

## Acknowledgements

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# EFFECTS OF CA3 BURSTS ON CA1 ACTIVITY EXAMINED THROUGH A SIMPLE CA3-CA1 SPIKING NETWORK

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The hippocampus and specifically the CA3-CA1 areas exhibit a variety of intrinsic rhythms that span frequencies from the slow theta range (4–8 Hz) up to fast ripples (150–200 Hz). Various computational models of different complexities have been developed in an effort to simulate such population oscillations and uncover their underlying mechanisms. Nevertheless most studies focus on specific rhythms generated in localised areas. They do not address more complicated phenomena such as the so called Sharp Wave-Ripple complex observed in CA1 EEG recordings, which is believed to be generated through the combination of large pyramidal dendritic depolarizations and fast synchronous interneuronal firing, induced by CA3 population bursts.

Here we present the combination of two simple but realistic models of CA3 and CA1 connected together in an effort to model Sharp Wave-Ripple complexes. Both network models are computationally simple one dimensional arrays of pyramidal and interneuron populations interacting only via fast AMPA and $\text{GABA}_A$ synapses. They were constructed using the 2-compartment Pinsky-Rinzel model for single pyramidal cells and the 1-compartment Wang-Buzsaki model for interneurons, reproducing the basic firing properties of hippocampal cells. Connectivity schemes and postsynaptic potentials are based on biological data, making the network topology as realistic as possible.

Our CA3 model is a highly recurrent network that reproduces a number of different features observed in real recordings or simulations of more sophisticated models (e.g. activity propagation in the disinhibited array, carbachol-induced oscillations (5–6 Hz) and others). Most importantly it exhibits theta-range near-synchronous population bursts that have been observed in CA3 slices and *in vivo*.

Recurrent pyramidal cell connections are absent in the CA1 network which is based mostly on the interaction between pyramidal cells and a strongly connected interneuronal network. The main rhythm reproduced here is the gamma oscillation of the pure interneuron population and its long range synchronization through the interaction with pyramidal cells. The two models are coupled together in a feed-forward CA3-to-CA1 scheme that mimics Schaffer collaterals.

In the full CA3-CA1 model, strong CA3 population bursts produce Sharp Wave-Ripple phenomena in CA1. Namely deep depolarizations in the dendritic layer accompanied by transient ~150–200 Hz field oscillations in the somatic layer. These oscillations appear to be a result of the interaction between the excitatory and inhibitory populations in CA1. Finally, since our model can successfully reproduce many basic features of the Sharp Wave-Ripple complex that have been described in various experimental studies, we believe that it is ideally suited to shedding further light on the potential mechanisms of such synchronous hippocampal events.

# THE BEREITSCHAFTS CROSS-POTENTIAL: SYNCHRONIZING NEURONAL ASSEMBLIES IN VOLITIONAL MOVEMENT

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Accumulating evidence from neurophysiological studies suggests that the motor cortex is not simply a static control structure, but it possesses a dynamic substrate that participates in motor learning and cognitive events. A remarkable example of the latter is the Bereitschaftspotential (readiness potential), an electroencephalographic manifestation of the cortical contribution to volitional movement in the precentral-parietal regions about 1000–1500ms *before* movement execution. We investigated the hypothesis that these components may involve motor synergies that manifests themselves in coherence patterns among neuronal groups, even if they are centimeters apart in the cortex. To this end electrocorticograms were recorded using subdural grid electrodes implanted in the motor cortex of human subjects. The subjects performed a self-paced button press task comprising (i) movement preparation; (ii) button presses. The electrocorticograms corresponding to components of movement (i)-(ii) were investigated by the use of different multivariate coherence metrics in the frequency domain, among others Partial Coherence, which prevents contamination from any non-local rhythms or common reference signal. This analysis revealed the presence of temporal synchronization among motor units in the theta, beta and gamma frequency ranges. Synchronous motor cortex oscillations in the beta range are most prominent during movement preparation, during actual movement they reduce. In the gamma range synchrony increases during and after button presses, which demand more sensorimotor integration. Furthermore, Directed Partial Coherence analysis revealed a lead of anterior regions to posterior regions throughout the time period of movement preparation and execution, suggesting that the frontal regions are in control of movement planning. We conclude that not only brain rhythms are modulated and assemblies of neurons are synchronized during specific phases of this simple volitional movement planning and execution, but also that such a phenomenon occurs in a consistent and more or less predictable fashion.

# POPULATION ACTIVITY IN A SPINAL MOTOR NETWORK MONITORED WITH EXTRA-CELLULAR MULTI-ELECTRODE RECORDINGS DURING MULTIPLE FUNCTIONS AND DURING LOCAL DRUG DELIVERY

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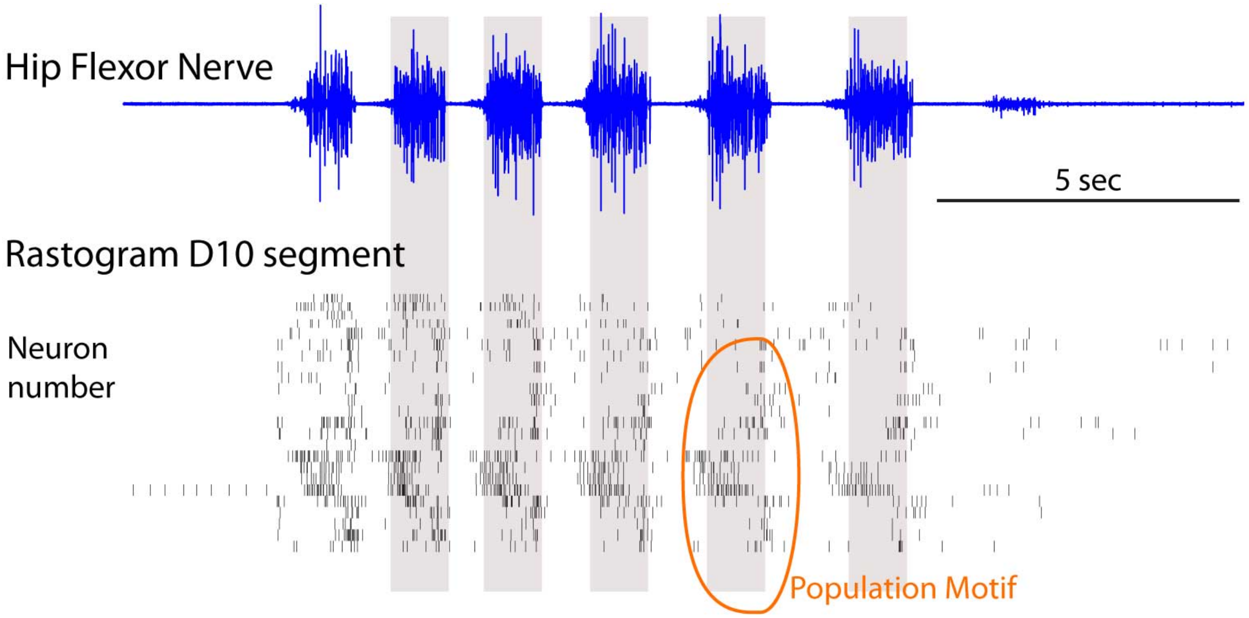
The mechanisms of central pattern generation in the spinal cord remain a puzzle. One major challenge is the large number of neurons involved in the generation of these motor patterns. In an attempt to address the issue of the population activity during motor activity we perform extra-cellular recordings with multi-electrode arrays in the semi-intact spinal cord of the adult turtle during fictive scratching (Keifer and Stein 1983). We find that most of the isolated units are rhythmically participating in the cyclic motor pattern (see figure). The recorded units have different but constant phase lag with respect to the hip flexor nerve in agreement with previous reports (see e.g. Berkowitz 2002).

Furthermore, in order to verify the role of inhibitory synaptic input during the scratch motor activity, we test the effects of local application of a glycinergic antagonistic agent (strychnine hydrochloride) delivered via a micro-fluidic probe. By testing if there is an increase in spike frequency in the active period, we evaluate the hypothesis that spike activity is driven by inhibition and excitation. Finally, we induce different motor behavior in order to determine spatial and temporal spike correlations and the extent of multi-functionalism of the population.

We conclude that this is a viable testing bed for studying the population dynamics of neurons involved in motor pattern generation of the scratch reflex of turtle.



# A COMMON-INPUT MODEL OF A COMPLETE NETWORK OF GANGLION CELLS IN THE PRIMATE RETINA

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Synchronized firing among retinal ganglion cells (RGCs) has been proposed to indicate either redundancy or multiplexing in the neural code from the eye to the brain. Two major candidate mechanisms of synchronized firing are direct electrical coupling and common synaptic input.

Recent modeling efforts (Pillow 2008) suggest that a generalized linear model with coupling between cells is able to accurately capture the synchronized spiking activity in parasol RGCs of the primate retina. But recent experimental work (Khuc-Trong 2008) indicates that electrical coupling between parasol cells is weak, and neighboring parasol cells share significant excitatory synaptic input in the absence of modulated light stimuli. These findings suggest that an accurate model of synchronized firing must include the effects of common noise.

Here we develop a new model of synchronized firing that incorporates the effects of common noise, and use it to model the light responses and synchronized firing of a complete network of a few hundred simultaneously recorded parasol cells. We use a generalized linear model augmented with a state-space model to infer common noise, spatio-temporal light response properties, and post-spike feedback which captures dependencies on spike train history. All model parameters are estimated by maximizing the likelihood of the spiking data. Common noise is modeled as an autoregressive process with a correlation time consistent with that observed by Rieke *et al*. We use fast methods for computing the estimated maximum a posteriori path of the hidden input, by taking advantage of its banded diagonal structure (Paninski 2009). To test the model, we compare average light response properties and two- and three-point correlation functions obtained from the model and the data. The model provides an accurate account of these properties.

We also use the model to decode the visual stimulus, by maximizing the posterior probability of the stimulus given the spiking activity and the model parameters, and compare the results to decoding based on a model with coupling between RGCs but with no common input. We find that the common input architecture is more robust with regard to spike time perturbations than a network with direct coupling between the RGCs, especially when synchronized firing is strong.

# HOW DO DISTINCT NEURONAL SUBPOPULATIONS IN THE CENTRAL AMYGDALA SHAPE THE FEAR RESPONSE? — A COMPUTATIONAL MODEL

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During a typical fear conditioning experiment a neutral stimulus is paired with a fearful one and after several trials the former acquires aversive properties. Such learning can be suppressed by repeated presentations of the initially neutral stimulus alone (fear extinction). The critical brain structures involved in these fear related processes are the lateral (LA), the basal (BA) and the central (CeA) nuclei of the amygdaloid complex. The CeA is a striatum-like structure containing almost exclusively GABAergic neurons [1]. It is known to be the major output nucleus of the amygdala and to control the fear response by its projections to the brainstem and hypothalamus.

To understand the interactions between the lateral (CeL) and medial (CeM) subdivisions of the CeA during fear conditioning and fear extinction, we built a spiking neuron network model of the CeA using the NEST simulator [2]. We modeled the CeA as a feedforward dis-inhibitory circuit, based on known anatomical and electrophysiological data. The input to the CeA was controlled by two distinct, fear and extinction specific neuronal subpopulations within the BA [3,4]. These inputs were crucial, as they altered the states of different subgroups within the CeA.

With our model we provide first insights about possible computations performed by the CeA. In particular, we show how CeL and CeM neurons might process fear and extinction related activity of the BA in order to shape the fear response.

## Acknowledgements

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# PERFORMANCE OF SUBDURAL ELECTROCOTICOGRAPHY ARRAYS TO RECORD AND STIMULATE THE SENSORIMOTOR CORTEX OF NONHUMAN PRIMATES

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**Background:** Subdural electrode arrays are routinely used for clinical evaluation of epileptic foci, and have been proposed as less invasive alternatives to intracortical electrodes in brain-machine interface (BMI) applications. We investigated long-term electrocorticography (ECoG) and cortical surface stimulation through subdural arrays in nonhuman primates (NHPs), and the tissue response to these arrays.

**Methods:** Two different types of subdural arrays of 4x8-electrodes were implanted on the sensorimotor [SM] cortex of 2 NHPs (3 hemispheres): a mini-grid (dimensions: 15x29 mm; exposed electrode diameter: 2 mm; inter-electrode distance: 3 mm) and two micro-grids (7x13.5 mm; 75 µm; 1.5 mm). Eight, mostly proximal, muscles of the arm were implanted with EMG wires. Multi-electrode ECoG was recorded simultaneously with contralateral arm EMGs while the animals performed unimanual reaching and grasping movements. Simultaneous ECoG and EMG signals were also recorded during free behavior in the cage using autonomous head-mounted electronics [Neurochip-2]. Electrical stimuli were delivered through different cortical electrodes and stimulus-evoked EMGs were recorded. In separate sessions, with the animal's arm resting inside a wrist torque sensor, stimulus-evoked torques were registered. Histology was examined for one of the three implants.

**Results:** ECoG from both types of arrays showed episodes of high-amplitude beta (15–25 Hz) oscillatory activity, interspersed with episodes of low-amplitude, high frequency (>50 Hz; HF) activity. Beta activity was present during rest and was suppressed prior to and during movement; a beta rebound was seen after the end of movement. Movement was associated with a broadband increase in HF power. A similar spectral pattern was seen with the Neurochip-2 recordings of ECoG and EMG during free behavior in the cage. Correlations between HF ECoG power and EMGs showed no evidence of a specific (one-to-one) relationship between individual cortical sites and muscles. There was, however, a topographic organization in the "preference" of HF ECoG for specific muscle groups, with gradual transitions between different cortical sites. Bipolar or Laplacian re-referencing, or analysis of different HF sub-ranges, did not significantly alter this pattern. Single-pulse electrical stimulation through the cortical electrodes evoked motor-evoked potentials (MEPs) at a latency of approximately 10 msec, with amplitudes that were greater during background EMG activity. Different cortical sites had different MEP thresholds, but all sites showed a similar distribution of evoked EMG responses across implanted muscles. Stimulating different cortical sites evoked similar wrist torques; for both types of arrays the prevalent evoked torque was combined wrist flexion, pronation and radial deviation. Sites with lower thresholds had greater movement-associated HF-ECoG power increases and larger HF power-EMG correlations. Histological examination of cortical tissue around the implant 7 months after placement revealed increased gliosis [GFAP staining], but no difference in neuronal density compared to healthy cortex.

**Conclusion:** Dense subdural arrays are effective interfaces for long-term recording of ECoG potentials and delivering electrical stimuli to the surface of SM cortex of NHPs. However, different sites showed limited specificity in the stimulus-evoked motor responses and the correlations between HF-ECoG and EMG for different proximal arm muscles. After 7 months, an array did not cause significant neuronal loss in the underlying cortex, but did induce a glial response.

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# SPECTRAL CONTAMINATION AND EFFICIENT REMOVAL OF SPIKE REMNANTS FROM LOCAL FIELD POTENTIALS

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Much of our understanding of brain function comes from extracellular recordings, which provide the experimenter with a high-resolution measure of spiking activity and local field potentials (LFPs). The former are derived from individual neurons, while the latter reflect activity in the local circuit near the tip of the recording electrode. The relationship between these two signals is a question of great importance to theories of cortical information processing, perception, memory, and to the development of neural prosthetic devices. Consequently there has been much recent investigation of the relationship between spikes and LFPs.

An important step in analyzing the relationship between two types of signals is to ensure that they can be estimated independently, and this step is particularly critical with extracellular recordings, as both the spikes and the LFPs typically originate from the same electrode. Most often the LFPs are derived by low-pass filtering and down-sampling the voltage signal, while the spikes are typically identified by template matching to a high-frequency waveform. However, it is possible that some low-frequency components of individual spikes remain present in the LFP after filtering, and such spectral contamination would lead to spurious correlations between the spike and LFP signals.

In this work we estimate the extent of spectral contamination from individual spikes and spike trains obtained from extracellular recordings, along with the effects of such contamination on the LFP spike-triggered average (STA), the spike-field coherence, spike-LFP phase locking histograms, as well as the prediction of spike timing from LFP features. The effects of contamination are quantified by ground-truth simulations of spike waveforms overlaid on random LFP-like signals (with various spike-to-LFP power level ratios and mean firing rates), and the results are confirmed with real recordings from the primate visual system.

Our results show that estimates of the relationship between LFPs and spikes can be considerably affected by spike contamination. We performed simulations in which spike waveforms were added to phase-randomized LFP signals, such that the spectral profile of the LFP was maintained but there was no actual LFP-spike relationship. Nevertheless, when spike removal was performed by low-pass filtering, our analysis showed artifactual spike-LFP STAs, even at low LFP frequencies (alpha or beta bands) and spurious phase-locking of spikes to LFPs. In contrast tuning curves in response to visual stimuli were not strongly affected by spike contamination, even at high frequencies (up to 140Hz), unless the spike-to-LFP power ratio was unnaturally high (>5dB). Similar results were obtained using real recordings with direction-tuned neurons from the primate visual system.

To address the issues associated with spike contamination we developed a novel Bayesian method that estimates veridical LFPs by removing action potential signatures from raw voltage signals. The approach involves a generative model for the voltage signal, composed of a low-frequency LFP component superimposed with spikes occurring at known times. The LFP then corresponds to the maximum a posteriori (MAP) estimate computed by an efficient conjugate-gradient algorithm. Hyperparameter values are determined through evidence optimization. We show that application of this method to both simulations and real data has a substantial impact on measures of the relationships between spikes and LFPs.

Our results show that processing of raw signals prior to estimation of LFPs and spikes can significantly affect the conclusions drawn about the nature and interactions of both signals.

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