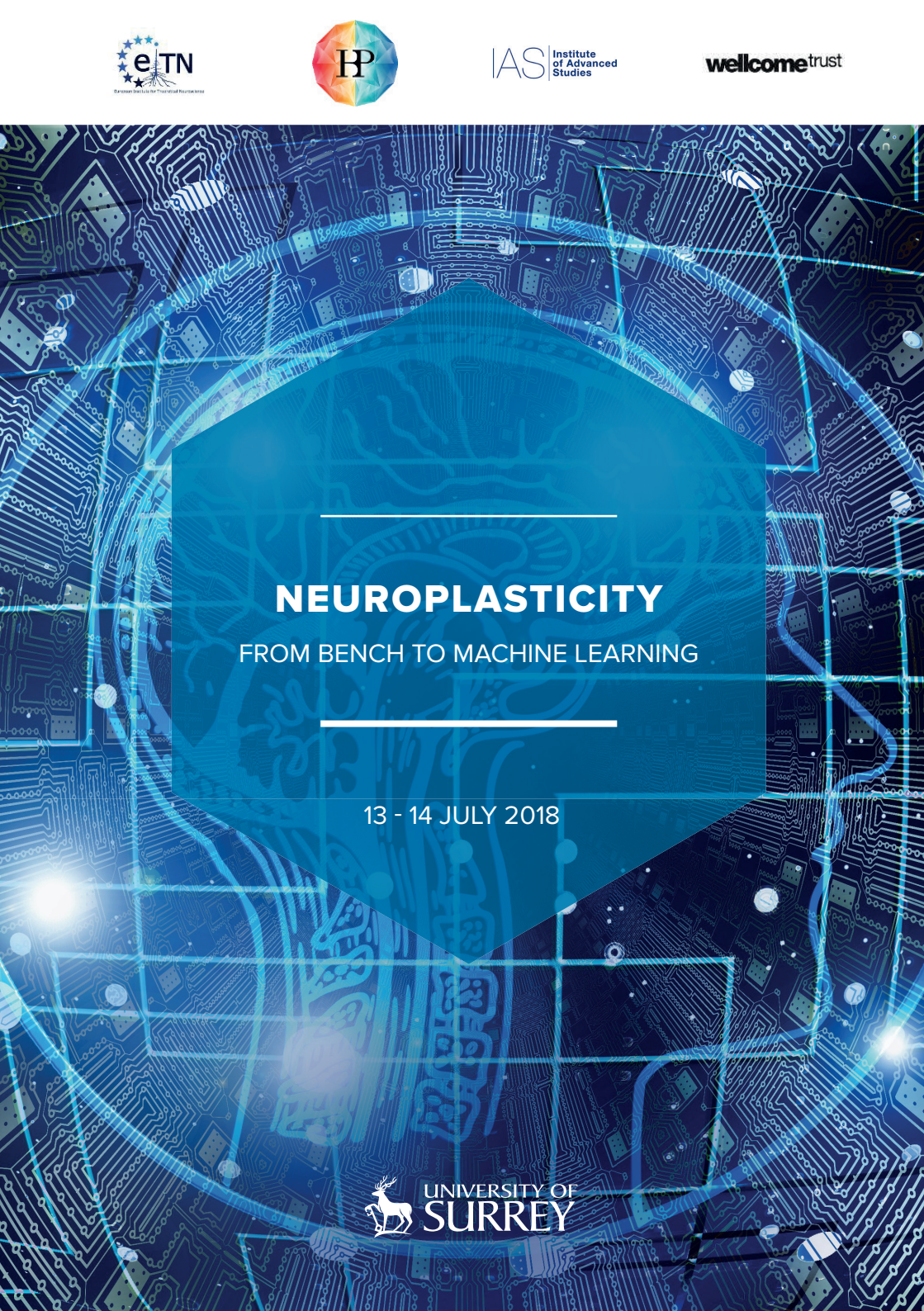

NEUROPLASTICITY
FROM BENCH TO MACHINE LEARNING
13 - 14 JULY 2018
UNIVERSITY OF SURREY

INTRODUCTION

Neuroplasticity is the fundamental process that allows our brains to adapt to changes in the environment and is at the basis of learning and memory. In the 50's, the neuropsychologist Donald O. Hebb described the fundamental principle of neural plasticity that stipulates that "neurons that fire together, wire together", recognising that brain connections undergo long-lasting changes in an activity-dependent manner leading to the well-established models of correlation-based synaptic plasticity. This model has contributed much to our current understanding of the physiology of neural plasticity and has fueled computational models used in artificial neural networks within machine learning without, however, achieving yet nature-like general intelligence and learning performances.

On one hand, it becomes increasingly clear that neuroplasticity can no longer be restricted to Hebb's rules as research keeps discovering new mechanisms which involves the so-called "third factors" (e.g. dendritic computations, glia, network dynamics). However the functional and computational interpretation of these phenomena and their utilisation in machine learning remains to be explored. On the other hand, the advent of "deep networks" in machine learning has allowed us to model artificial neural networks that perform highly complex tasks (e.g. chess). But to date, none of these modeling approaches competes with general human or animal intelligence in terms of cost-effectiveness.

This workshop on Neuroplasticity will focus on the recent developments in neural plasticity and machine learning and their mutual inspiration. By bringing together international and national scientists, we hope to stimulate discussions and new interdisciplinary collaborations to bridge the gaps between experimental and computational approaches models of neuroplasticity.

Organisers:

Dr Andre Grüning,
Department of Computer Science,
FEPS, University of Surrey
Dr Julie Seibt,
Surrey Sleep Research Centre,
FHMS, University of Surrey

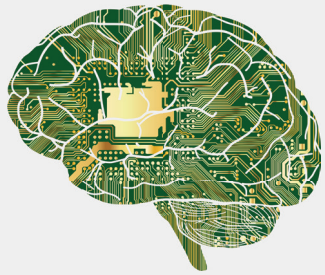
PROGRAMME

DAY 1 FRIDAY 13 JULY
LECTURE THEATRE J

8:30 am	**Registration and coffee**
9 am	**Welcome** Derk-Jan Dijk, Head of the Surrey Sleep Research Centre, University of Surrey
9:10 am	Giorgos Kastellakis **Linking memories across time via excitability and synaptic tagging**
9:55 am	Conor Houghton **Anti-Hebbian learning with Hebbian spike timing dependent plasticity**
10:40 am	**Coffee**
11:10 am	Matthew Larkum **Looking for memory in L1 of the cortex**
12 pm	**Lunch/Poster**
2 pm	Tiina Manninen **Computational models of astrocytes and neuron-astrocyte interactions to promote understanding of synaptic function and dysfunction**
2:45 pm	Cyril Hanus **Local protein synthesis and atypical glycosylation diversify the properties of dendritic ion channels**
3:30 pm	**Coffee**
4 pm	Liam McDaid **Biophysical Models of Astrocyte-Neuron Communications**
4:45 pm	**Panel Discussion**
7pm	**Workshop Dinner (Olivo, Guildford)**

DAY 2 SATURDAY 14 JULY
LECTURE THEATRE J

8:30 am	**Registration and coffee**
9 am	Keith Hengen **From neurons to networks: homeostatic principals of self-organization in the brain**
9:45 am	Mike Davies **Loihi: Putting the "Learning" in Machine Learning Processors**
10:30 am	**Coffee**
11 am	Katharina Wilmes **Interneuron circuits for top-down guided plasticity of sensory representations**
11:45 am	**Short Talk:** Dominik Dold **From Euler-Lagrange to time-continuous error backpropagation in cortical microcircuits**
12:10 pm	**Lunch/Poster**
1 pm	**Lunch**
2:30 pm	Friedemann Zenke **Moving beyond random spiking neural networks by surrogate gradient descent**
3:15 pm	Brendon Watson **Sleep regulation of the distribution of cortical firing rates**
4 pm	**Coffee**
4:30 pm	Dave Lester **Learning and Plasticity on SpiNNaker**
5:15 pm	**Concluding remarks**



SPEAKER ABSTRACTS

LINKING MEMORIES ACROSS TIME VIA EXCITABILITY AND SYNAPTIC TAGGING

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The question of how memories are organized in our brains is one of the biggest research directions in neuroscience, which has recently received renewed focus thanks to the advent of molecular techniques that allow the detailed monitoring of brain cells during memory tasks [1, 2]. Memories are believed to be imprinted in the brain as engrams, which consist of specific, but not localized changes in the synapses between neurons, as well as changes in the neurons themselves. The molecular mechanisms that mediate these changes are active not only at the time when a memory is being acquired, but long after, allowing memories to interact with each other. During the process of engram formation and memory allocation, neurons and synapses are recruited to encode a specific memory. Recent experiments have shown that CREB activation determines the probability of neuronal recruitment in a memory engram via intrinsic excitability. In addition, memories that are temporally close have been found to be encoded in overlapping populations of neurons in CA1. Other experiments highlight the role of synaptic tagging and capture (STC) during memory allocation as a mechanism for binding together memories, but also for inducing competition between engrams for the capture of plasticity related proteins (PRPs).

We have previously created computational models to probe these mechanisms of memory allocation and their possible roles in memory binding [3]. Our models incorporate the phenomenology of plasticity-related mechanisms that act at multiple spatial and temporal scales. Using these models we show how STC and excitability create temporal windows for the overlapping allocation of memories to populations. We find that this effect is dependent on the locus of protein synthesis, and that somatic PRP synthesis favours population sparsity. When pairing strong and weak memories, memory allocation creates overlapping ensembles of neurons and synaptic clusters in dendrites which facilitates the linking of temporally related memories and the rescuing of weak memories.

During memory allocation, synaptic turnover takes place, and it has been found that dendrites that exhibit higher synaptic turnover pre-learning have increased synaptic clustering post-learning [4]. We extended our plasticity model to incorporate the role of synaptic turnover during memory allocation. Our model corroborates the findings of increased synaptic clustering and also predicts that it increases the population sparsity after memory encoding, indicating that synaptic turnover may affect memory discriminability. Finally, these findings suggest roles for excitability and STC in learning which prime and facilitate learning in neural networks. We therefore examine the role of excitability in neural networks and the conditions under which excitability may facilitate or accelerate learning.

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ANTI-HEBBIAN LEARNING WITH HEBBIAN SPIKE TIMING DEPENDENT PLASTICITY

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Hebbian spike timing dependent plasticity strengthens the synapse from one neuron to another if the spikes from the first neuron tend to precede the spikes from the other. However, this doesn't always lead to Hebbian learning; here two examples will be presented of anti-Hebbian learning from spike timing dependent plasticity.

LOOKING FOR MEMORY IN LAYER 1 OF THE CORTEX

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The hippocampus plays a vital role in transforming experience into long-term memories that are then stored in the cortex. However, the cellular mechanisms that designate how single neurons become part of a memory trace remain unknown. Part of the difficulty in addressing this question is the distributed nature of the cortical connectivity that results in the "engram" manifesting at synapses throughout the entire cortex. Here, I present recent evidence suggesting that connections arising in the hippocampus terminate (via intermediate areas) predominantly in layer 1 of the neocortex. This represents a nexus point for investigating memory. Such input must intermingle with long-range, feedback information and the highly electrogenic tuft dendrites of pyramidal neurons. This presentation will discuss the "Dendrite Hypothesis" that attempts to reconcile these facts, positing that all roads lead to layer 1. I will discuss how this may make way for a general theory of memory formation.

COMPUTATIONAL MODELS OF ASTROCYTES AND NEURON-ASTROCYTE INTERACTIONS TO PROMOTE UNDERSTANDING OF SYNAPTIC FUNCTION AND DYSFUNCTION

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Our understanding of astrocytes in brain function and dysfunction has increased substantially over the past two years. Although several experimental controversies exist, new roles of astrocytes have been proposed, including roles in synaptic development, plasticity, and learning [1–3]. We have addressed the roles by studying computational astrocyte and neuron-astrocyte models. We have characterized, categorized, and evaluated about a hundred models developed for single astrocytes, astrocyte networks, neuron-astrocyte synapses, and neuron-astrocyte networks [4]. We have also evaluated in detail some of the models by trying to implement them based on the knowledge in the original publications and reproduce the original results, as well as compare the models to each other [5–6]. Based on these studies, we found out that computational studies many times make somewhat naive assumptions and use data different from astrocytes. New models have been developed without explaining how they diverge, if they diverge, from the previously published models and what new predictions the models are able to show on top of the previously published models [4]. Development of previously published models, as well as the reproducibility, replicability, and comparability issues has been made difficult and time-consuming by not providing all the model details in the original publications and not providing the model implementations in the available model repositories [4–6]. We especially want to underline the use of common description formats when defining models in the publications and description languages when providing models in model repositories. Using our evaluation studies of astrocyte models as guidelines, we have developed neuron-astrocyte synapse models for cortical synapses [7]. In the future, we attempt to construct both detailed and reduced models of neuronastrocyte interactions for different brain areas, which will hopefully provide additional clarifications to the controversies presented in different experimental studies [1–3]. In this talk, I will present the state-of-the-art in modeling astrocyte functions, discuss the reproducibility and replicability issues related to computational astrocyte models, and outline future needs to assist the understanding of how astrocytes may contribute to different synaptic functions and dysfunctions.

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LOCAL PROTEIN SYNTHESIS AND ATYPICAL GLYCOSYLATION DIVERSIFY THE PROPERTIES OF DENDRITIC ION CHANNELS

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For us to learn and form memories, our neurons must selectively modify the composition and properties of a few selected synapses among the tens of thousands synapses that they maintain with other neurons. To achieve this daunting task, neurons have evolved novel means to regulate and exploit the core cellular machinery and, for example, locally synthesize synaptic receptors to directly functionalize specific synapses during learning and memory formation.

Over the past ten years, we have characterized multiple mechanisms that enable neurons to locally process membrane and secreted proteins and traffic them to the specific segments of dendrites and synapses where they are needed. Intriguingly in doing so, we found that while neuronal dendrites contain all the machinery that is needed for the biogenesis of secretory proteins, dendrites are devoid of generic Golgi membranes. Because one of the key function of the Golgi apparatus is to glycosylate proteins - i.e. to modify the chemical composition of these proteins by addition of complex sugars - this led us to investigate how the unique organization of the neuronal secretory pathway impacts N-glycosylation and hence the dynamics and functional properties of synaptic proteins.

We hence discovered that, as a result of local protein synthesis and Golgi bypass, surface expressed neurotransmitter receptors and virtually all the key proteins of the neuronal surface display N-glycosylation profiles that are typically only found on immature intracellular proteins in the endoplasmic reticulum in other cell types. This atypical N-glycosylation regulates the turnover and biophysical properties of synaptic receptors, revealing a previously unrecognized mechanism that controls the sensing properties and plasticity of the neuronal membrane.

BIOPHYSICAL MODELS OF ASTROCYTE-NEURON COMMUNICATIONS

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Astrocytes, the most abundant type of glial cell in the brain, are important contributors in metabolic maintenance and are also involved in neuronal activity and information processing in the nervous systems. Current research has shown that they have a large number of receptors which suggests that astrocytes exchange information with neurons thereby influencing their behaviour. Approximately 50% of synapses have an intimate connection between astrocytes and neurons and consequently synapses exchange signals at three terminals, hence the name tripartite synapse. Astrocytes have been found to possess binding sites for endocannabinoids and are also reportedly involved in the uptake of Glutamate and Potassium. This talk will present models that capture the biophysical mechanisms that underpin the coordination of synaptic activity with many homeostatic reactions of astrocytes and additionally propose a new mechanism that could explain the formation of Sodium and Potassium microdomains at the perisynaptic cradle. The formation of potassium microdomains will be shown to point to a new mechanism for Potassium clearance from the synaptic cleft.

FROM NEURONS TO NETWORKS: HOMEOSTATIC PRINCIPALS OF SELF-ORGANIZATION IN THE BRAIN

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Input specific modulation of synaptic strength (e.g. Hebbian plasticity) is severely destabilizing to complex neural networks, especially those with recurrent connectivity. This is difficult to reconcile with the impressive stability of neural function across the lifetime of an organism. While homeostatic mechanisms have been proposed stabilize the activity of single neurons, it is unclear how the complex interactions of many neurons, i.e. network dynamics, are maintained stably. The Hengen Lab addresses questions of active self-organization, stable function, and the relationship between neural dynamics and stable behavior on ethologically relevant timescales of weeks to months. The lab relies upon high density recordings of many individual neurons in freely behaving animals to examine dynamics at the micro, meso, and macro scale. This work necessarily involves machine learning, synthetic networks, and theoretical approaches.

LOIHI: PUTTING THE “LEARNING” IN MACHINE LEARNING PROCESSORS

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In September of 2017, Intel announced its Loihi neuromorphic research chip. This novel processor implements a microcode-programmable learning architecture supporting a wide range of neuroplasticity mechanisms under study at the forefront of computational neuroscience. By maintaining the same locality of information processing and integrated memory-compute architecture as the brain, Loihi promises to provide highly efficient and scalable learning performance for supervised, unsupervised, reinforcement-based, and one-shot paradigms. This talk provides an overview of the Loihi architecture and preliminary results towards our vision of low power and real-time on-chip learning.

INTERNEURON CIRCUITS FOR TOP-DOWN GUIDED PLASTICITY OF SENSORY REPRESENTATIONS

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Inhibitory interneurons form canonical circuit motifs across brain areas and have been repeatedly shown to play a role in learning and memory. There are several ways in which interneurons could be involved in learning by shaping synaptic changes. In my talk, I will present recent work on how interneuron circuit structure could guide synaptic plasticity in the context of stimulus-reward association learning: Humans and animals are remarkable at attending to stimuli that predict rewards. While the underlying neural mechanisms are unknown, it has been shown that rewards influence plasticity of sensory representations in early sensory areas (Poort et al. 2015, Goldstein et al. 2013, Khan et al. 2018). Hence, top-down reward signals can modulate plasticity in local cortical microcircuits. However, synaptic changes require time, but rewards are usually limited in time. Because the two happen on different time scales, it is unclear how reward signals interact with long-term synaptic changes. We hypothesised that interneuron circuit, which are key players during learning and memory (e.g. Letzkus et al. 2011, Fu et al. 2014), bridge the timescales. We hence investigated how temporary top-down modulation by rewards can interact with local excitatory and inhibitory plasticity to induce long-lasting changes in sensory circuitry. We constructed a model of layer 2/3 mouse visual cortex consisting of excitatory pyramidal neurons, somatostatin (SST)-positive, parvalbumin (PV)-positive and vasoactive intestinal peptide (VIP)-expressing interneuron types. In our model, a connectivity structure arises between interneurons during the reward phase. After the reward phase, this structure disinhibits pyramidal neurons during the previously rewarded stimulus. This enables excitatory connectivity to refine after the reward phase, which results in an increased representation of the rewarded stimulus. In summary, I will demonstrate how interneuron networks can store information about relevant stimuli to instruct long-term changes in excitatory connectivity beyond the presence of reward signals.

FROM EULER-LAGRANGE TO TIME-CONTINUOUS ERROR BACKPROPAGATION IN CORTICAL MICROCIRCUITS

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How synaptic connections in the cortex are locally modified to learn to jointly solve complex tasks like playing an instrument is still an open question commonly known as the "credit assignment problem". Recently, it has been proposed that the brain may approximate the widely-used backpropagation algorithm ("backprop"; Rumelhart et al. 1986) during learning (Guerguiev et al. 2017, Scellier et al. 2017, Sacramento et al. 2017) which is the key ingredient behind the recent Deep Learning revolution (LeCun et. al 2015). However, such models either rely on the neuronal dynamics being in a stationary state before synaptic plasticity is induced or learning is separated into two distinct phases. This in turn prevents learning from sensory input streams with time-continuous structure. Here we present a novel theoretical approach that mitigates these problems.

Our approach is inspired by the predictive coding paradigm proposed in earlier work (Rao and Ballard 1999, Scellier et al. 2017), in which neuronal and synaptic dynamics are defined as gradient descent on an energy function. We assume instead a least-action principle, from which the dynamics follow as Euler-Lagrange equations of an energy function with respect to the discounted future neuronal voltage, i.e., dynamics are derived based on the predicted future neuronal activity rather than the instantaneous activity ("Prospective Coding", Brea et al. 2016). The resulting neuronal dynamics can be interpreted as multi-compartment with Hodgkin-Huxley-like dynamics, allowing neurons to phase-advance their somatic input and hence undo temporal delays introduced by somatic and dendritic low-pass filtering (Fig. 1A).

Similar to previous work (Sacramento et al. 2017), synaptic plasticity in our model is driven by a local prediction error at distal dendrites that results from the discrepancy between bottom-up activities and top-down feedback (Fig. 1B). The prediction errors are calculated locally by lateral inhibitory interneurons, which try to cancel the top-down feedback. If part of the top-down feedback cannot be explained away by the lateral interneurons, this results in a non-zero prediction error at distal dendrites, driving plasticity on bottom-up connections at basal dendrites of the same neuron to reduce the prediction error to zero. The coupled neuronal and synaptic dynamics can be shown to approximate time-continuous backprop in recurrent cortical microcircuits. To demonstrate the learning capabilities, we trained networks to recognize handwritten digits from the MNIST dataset using a setup with (i) coupled forward and interneuron weights, reaching 97.64% classification rate (Fig. 1C), and (ii) plastic interneuron weights, currently reaching 95.44% (Fig. 1D).

Thus, our theory provides a principled view of neuronal dynamics and plasticity rules, further narrowing the gap between biophysical plasticity rules and abstract learning algorithms while being consistent with features of cortical microcircuits such as Hodgkin-Huxley-like mechanisms, multiple compartments and cell-specific inhibition.

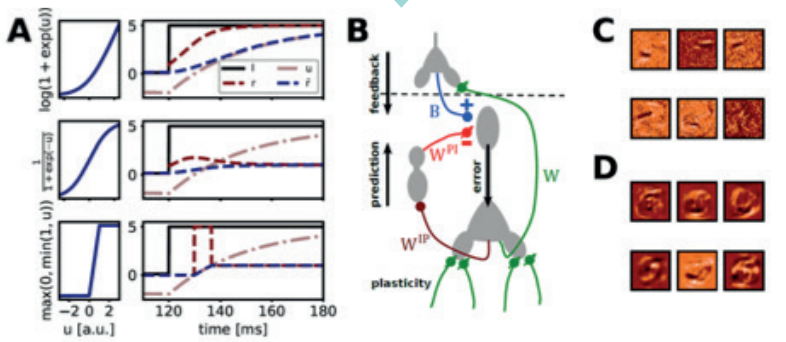

Figure 1: **(A)** Response of a neuron given a step current I (black, right) for different transfer functions φ (blue, left). The input gets integrated at the soma (pink), but the instantaneous response r (red) is phase-advanced, satisfying the relation $r = \bar{r} + \tau\dot{\bar{r}}$ with $\bar{r} = \varphi(u)$ (blue). **(B)** Cortical microcircuit encoding errors to drive plasticity. **(C)** Receptive fields learned with 784-800-10 pyramidal neurons, 10 interneurons and tied weights, i.e., $(W^{PI})^T = B^T = W^{IP} = W$. **(D)** Receptive fields learned with 784-500-10 pyramidal neurons, 40 interneurons and plastic weights, i.e., weights are not tied and (W, W^{PI}) are plastic, (B, W^{IP}) constant.

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MOVING BEYOND RANDOM SPIKING NEURAL NETWORKS BY SURROGATE GRADIENT DESCENT

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Computation in the brain is in large part performed by spiking neural networks. However, currently we neither understand how biological spiking neural circuits compute and nor how to instantiate such capabilities in artificial spiking network models. In my talk I will focus on training recurrent and multi-layer and recurrent artificial spiking neural networks by minimizing cost functions. Crucially, in the spiking setting standard gradient-based optimization methods fail because gradients vanish when propagated through a deterministic spiking threshold. To overcome this limitation, I will introduce the "SuperSpike trick" and use it to derive surrogate gradients. These approximate gradients can then be used to train spiking networks to perform nonlinear computations in the temporal domain. Further, I will demonstrate the effectiveness of this approach on benchmarks and discuss biologically plausible reductions of the algorithm.

NEURAL OSCILLATIONS, BRAIN STATES AND FIRING DYNAMICS

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The brain travels through varying oscillatory states as animal behavior varies, including and especially changes in sleep-wake status. Sleep is thought to mediate both mnemonic and homeostatic functions. However, the mechanism by which this brain state can simultaneously implement the 'selective' plasticity needed to consolidate novel memory traces and the 'general' plasticity necessary to maintain a well-functioning neuronal system is unclear. Recent findings show that both of these functions differentially affect neurons based on their intrinsic firing rate, a ubiquitous neuronal heterogeneity. Furthermore, they are both implemented by the NREM slow oscillation, which also distinguishes neurons based on firing rate during sequential activity at the DOWN➔UP transition. These findings suggest a mechanism by which spiking activity during the slow oscillation acts to maintain network statistics that promote a skewed distribution of neuronal firing rates, and perturbation of that activity by hippocampal replay acts to integrate new memory traces into the existing cortical network.

LEARNING AND PLASTICITY ON SPINNAKER

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SpiNNaker was originally designed to support fixed connection networks of LIF neurons with a fan-in/fan-out of just 1,000. More recent work has shown that these limitations can be traded off against one another and that fan-in/outs of 10,000 are possible, that very sparse networks can be handled, and finally that many different plasticity mechanisms can be successfully implemented. I will be discussing the various models that I'm aware of, that have already been implemented, and I am confident that as a result of this talk I will discover more models that have been implemented. Hopefully, as a result of this, we can put together a discussion document reviewing these models.

POSTER ABSTRACTS

DOES MEDITATION CHANGE HOW WE PROCESS FEEDBACK

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Focused attention meditation (FAM) practices are cognitive control exercises where meditators learn to maintain focus and attention in the face of distracting stimuli. Previous studies have shown that FAM is both activating and causing plastic changes to the mesolimbic dopamine system and some of its target structures, particularly the anterior cingulate cortex (ACC) and striatum. Feedback based learning also depends on these systems and is known to be modulated by tonic dopamine levels. Capitalizing on previous findings that FAM practices causes dopamine release, the present study shows that FAM practitioners display a more positive feedback learning bias (FLB) than matched controls on a probabilistic learning task. Furthermore, they have smaller feedback related negativity (FRN) than controls. Crucially, these effects scale with FAM experience for FRN. A possible explanation for this effect is that FAM practice causes persistent increases in tonic dopamine levels over time which results in the observed changes in feedback processing

BIOLOGICAL SOLUTIONS TO THE MIXING PROBLEM

Luziwei Leng1*, Agnes Korcsák-Gorzó1*, Roman Martel1, Oliver Breitwieser1, Ilja Bytschok1, Walter Senn2, Johannes Schemmel1, Karlheinz Meier1, Mihai A. Petrovici1,2*

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When presented with ambiguous sensory input, humans are often able to consider different, mutually incompatible scenarios that are at least partly consistent with their perception. The ability of making such Bayesian judgements has been an interesting topic both in machine learning and biology. Generative neural networks have been widely applied to various inference tasks, text and video generation (Rezende et al., 2014; Vinyals et al., 2015; Vondrick et al., 2016). Experimental evidence suggests a similar computational interpretation of ongoing activity in the brain (Fiser et al., 2010; Hindy et al., 2016; Jezeket al., 2011).

Under the generic assumption of contrastive Hebbian learning, traditional probability based models such as Boltzmann machines often attain multimodal energy landscapes with deep attractor basins separated by high energy barriers. This causes the network to often become trapped in local minima, greatly reducing the diversity of produced patterns (Fig.1 D).

Classical algorithms solve this problem by employing annealing or tempering techniques (Kirkpatrick et al., 1983; Salakhutdinov, 2010), which flatten the energy landscape to help the network jump out of local modes (Fig.1 A). Based on previous works on spike-based generative models (Petrovici et al., 2015, 2016; Probst et al., 2015), we demonstrate that this principle can be implemented in spiking neural networks with neural oscillations. Here, we use networks with leaky integrate-and-fire neurons to learn and reproduce handwritten digits (MNIST). We show that an appropriate modulation of the background Poisson noise leads to a rescaling of the energy landscape analogous to simulated tempering. A mapping between the temperature defined for networks with abstract units and the Poisson noise rate in spiking networks was established. A rate variation scheme based on this principle facilitates the network to jump out of local minima and mix quickly between different modes, thereby converging faster towards the target distribution (Fig.1 B). We thereby suggest a functional role of the macroscopic neural oscillations observed in the cortex in modifying a network's attractor landscape for faster Bayesian computation.

While such tempering approaches are a well-established technique, they usually come at a significantly increased computational cost and require global state updates. In the second part of our study, we show that similar results can be achieved in spiking networks endowed with short-term plasticity (STP), which improves mixing by changing the active local attractor (Leng et al., 2017) (Fig.1 A, C).We study a combination of potentiation and depression which first deepens the local minimum, creating a high-contrast image, followed by a rise that pushes the network to jump out of the local attractor (Fig.1 C). Additionally, we discuss how these networks can even outperform tempering-based approaches when the training data is imbalanced (Fig.1 D). We thereby uncover a powerful computational property of biologically inspired, local, spike-triggered synaptic dynamics based simply on a limited pool of synaptic resources, which enables them to deal with complex sensory data.

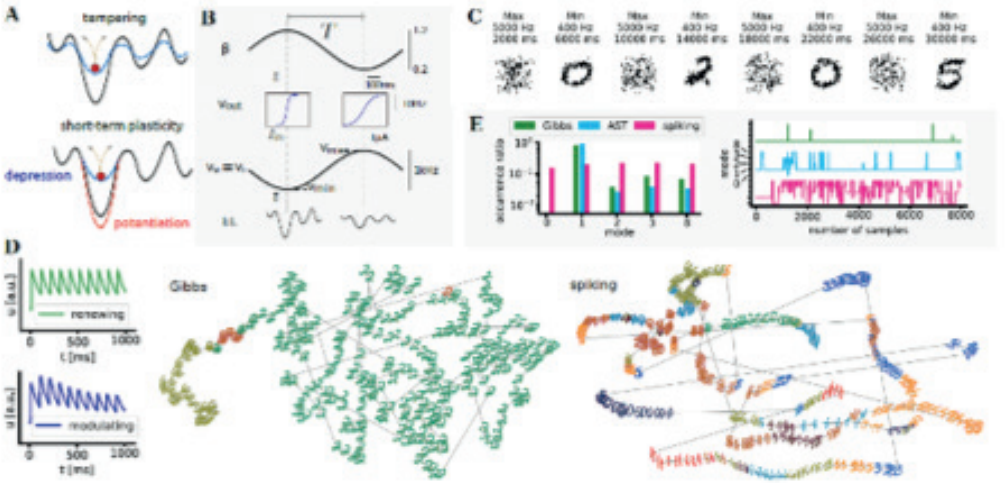

Figure 1: (A) To facilitate mixing, tempering methods globally rescale the energy landscape with a temperature (top). In contrast, STP can be viewed as only modulating the energy landscape locally, thereby only affecting the currently active attractor (bottom). (B) The rate variation scheme of the background noise (with balanced excitation and inhibition) follows the shape of a sine wave, which is mapped to the inverse temperature (β) domain. An increasing rate decreases the slope of the activation function of each individual neuron, and flattens the global energy landscape. (C) MNIST digits generated by a spiking network exposed to oscillatory noise input: The network forms clearly recognizable digits in the minima, while using the high-noise maxima to jump between different modes. (D) Left: Renewing synapses (top) would keep the average interaction between pairs of neurons constant, while plastic synapses (bottom) with appropriate Tsodyks-Markram (Fuhrmann et al., 2002) parameters first strengthen, then weaken the effective interaction. This causes a local change in the energy landscape, first deepening the energy trough and sharpening the produced image, followed by a local flattening of the energy landscape which pushes the network state into a different mode. Middle and right: tSNE (Maaten and Hinton, 2008) plots of images produced by Gibbs sampling and a spiking neural network with STP over 1800 consecutive samples. For every 6th of these samples, an output image is shown. Consecutive images are connected by grey lines. Different colours represent different image classes. Note that tSNE inherently normalizes the area of the 2D projection; the volume of phase space covered by the Gibbs chain is, in fact, much smaller than the one covered by the spiking network. (E) Comparison of Gibbs and AST samplers with STP-endowed spiking networks for imbalanced training data (820 digits of class "1" and 45 from the "0", "2", "3" and "8" classes). Left: Histogram of relative time spent in different modes. Right: Mode evolution over consecutive samples. The STP-induced weakening of active attractors balances out their activity, thereby negating the inherent imbalance induced by the training data and leading to fast mixing between different modes. In contrast, traditional sampling algorithms are trapped in the majority mode.

DEHYDRATION INDUCED NEUROGLIAL PLASTICITY BETWEEN VASOPRESSIN NEURONS AND ASTROCYTIC PROCESSES IN SUPRAOPTIC AND PARAVENTRICULAR NUCLEI OF MERIONES SHAWI HYPOTHALAMUS AND EXHIBITED HIGH EXPRESSION OF THE KIDNEY WATER CHANNEL: AQUAPORINES-2

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Supraoptic (SON) and paraventricular (PVN) nuclei are part of the hypothalamic system, they constitute the main source for vasopressin (AVP) and they represent obvious examples of activity-dependent neuroglial plasticity. Under sever conditions of dehydration, AVP neurons, release AVP which stimulates the expression of the kidney water channel named aquaporines type 2 (AQP-2), necessary for the reabsorption of water and reduces significantly the dieresis. The aim of the present investigation is to clarify the underlying central and peripheral mechanisms allowing the desert rodent Meriones shawi to regulate its body water content and resist to dehydration. Thus, GFAP, AVP and AQP-2 immunoreactivities were used successively as activation indicators of astrocytes, AVP neurons and medulla kidney AQP-2. Hence, we studied the immunoreactivity in various hydration states: water ad libitum, one and three months of water deprivation. Our results showed that dehydration of Meriones induced a significant decrease of GFAP accompanied by a significant increase of AVP immunoreactivities, the latter concerns both cell bodies and fibers in the same hypothalamic nuclei SON and PVN. Peripherally, a significant increase of AQP-2 immunoreactivity in the medullar part of Meriones kidneys was simultaneously seen. These results show that both astrocytes and AVP neurons display a remarkable structural and physiological plasticity on both SON and PVN with an excessive release of AVP, which acts probably on AQP-2 allowing probably to Meriones a great ability to water retention. These various changes at both central and peripheral levels might be the basis of control of body water homeostasis, providing to M. shawi a strong resistance against dehydration.

MRI BIOMARKERS FOR CANINE CHIARI MALFORMATION ASSOCIATED PAIN AND SYRINGOMYELIA

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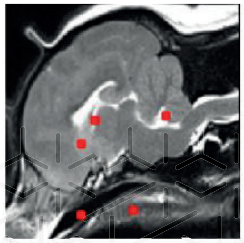
Canine Chiari malformation (CM) is prevalent in brachycephalic toy breeds including the Cavalier King Charles spaniel (CKCS). Although some dogs are asymptomatic, CM can be associated with pain and secondary syringomyelia (SM). Morphometric studies on traditional MRI can distinguish between clinical groups. However is not easy to translate findings from research to clinical practice.

The aim of this study was to extract imaging markers from MRI in relation to CM associated pain (CM pain) and SM in adult CKCS dogs. This study was split into two analyses: comparing a CM pain class to asymptomatic CM controls, and comparing a symptomatic SM class to controls. The dogs were diagnosed based on clinical signs and MRI. A midline sagittal MRI of the head and neck of a CKCS from the control group was chosen as a reference. The midline sagittal MR images of 77 dogs were mapped onto the reference MRI using DEMONS (non-linear) image registration, producing a 2D deformation map for each case. For each pixel, direction and magnitude of the mapping deformation were computed. Potential biomarkers were identified amongst these descriptors using a machine learning approach consisting of a feature selection algorithm, to identify candidate markers of CM pain or SM, and a kernelised Support Vector Machine classifier, to analyse the ability of these to successfully separate controls and clinical cases. This resulted in an area under the curve (AUC) of 81.51 for CM pain and 86.10 for SM. The analysis identified 5 markers for CM pain (in the regions of the nasopharynx, soft palate, caudal nucleus, hypothalamus and 4th ventricle) and 5 markers for SM (in the regions of soft and hard palate interface x 2, soft palate, trochlear nucleus, and corpus callosum) (figure 1).

Identification of biomarkers can be used to develop an objective tool for diagnosis.

Figure 1: Identified markers for (A) CM pain and (B) Syringomyelia.



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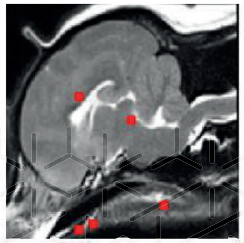

B

EXPERIENCE-DEPENDENT MODULATION OF CORTICAL DENDRITIC ACTIVITY ACROSS WAKE AND SLEEP

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During sleep, structural and functional changes of dendrites have been proposed to serve as the substrate of memory storage in the cortex (1). Dendrites of layer 5 neurons (L5 dendrites) integrate countless synaptic inputs and, owing to their intrinsic properties, can express localized synaptic plasticity mechanisms (2). We have previously shown that, during sleep, calcium (Ca2+) activity of L5 dendrites is modulated by specific neuronal oscillations during non-rapid-eye movement (NREM) sleep, called spindles (3). This work provided a novel link between the previously observed increase in spindles after learning and the requirement for dendritic activation during NREM sleep for memory consolidation (4). However, rapid-eyemovement (REM) sleep also seems to be important for experience-dependent structural plasticity and Ca2+ increase in L5 dendrites (5). In in this study we aim to gain a better understanding of how sleep stages, neuronal oscillations and activity of different dendritic compartments interact to support sleep-dependent plasticity.

We used two-photon Ca2+ imaging of L5 somata and apical dendrites, specifically the apical tuft and apical shaft, across active wake [AW], quiet wake [QW], NREM and REM sleep. Given the pivotal role of precisely timed dendritic inhibition in plasticity, we also imaged somatostatin (SST) interneurons that are known to target apical dendrites. Combining Cre-dependent expression of GCaMP6s in L5 (Rbp4-Cre, n = 4) and SST transgenic mice (SST-Cre, n = 4), we imaged a total of 706 L5 dendrites, 125 L5 somata and 88 SST interneurons. To assess the influence of experience, we compared Ca2+ activity during a baseline period and after three hours of exposure to an enriched environment (EE) the next day. EE exposure is known to trigger robust cortical plasticity during sleep. Both imaging sessions were performed at the beginning of the light phase (i.e. 8am) when sleep requirement is maximal.

Preliminary results revealed that dendrites and somata (SST and L5) exhibit large variability in Ca2+ activity during AW and REM sleep, compared to QW and NREM sleep. On average, however, there is a decrease in activity from AW to QW to NREM sleep for dendrites and somata. Interestingly, during REM sleep, SST and L5 somata further decrease their activity, while dendritic Ca2+ showed a marked increase. EE exposure had a significant effect on Ca2+ activity in both SST neurons and dendrites. Across states, dendrites increased their activity most during NREM and REM sleep, while SST neurons showed the most significant increase during wakefulness (AW and QW). In contrast to dendrites, SST neurons decrease their activity during NREM following EE, supporting the disinhibition of dendrites following experience during that sleep stage.

Further, we investigated the influence of sleep oscillations on synchronization of Ca2+ activity. Preliminary results suggested that sigma oscillations (i.e. spindles) are correlated with synchronization of both dendrites and SST neurons during NREM, with a differential effect across the dendritic tree.

So far, our results confirm previous results showing a decrease in activity in SST neurons across brain states (6) and an experience-dependent increase in dendritic activity during REM sleep (5). Noteworthy, however, was the remarkable dichotomy of L5 dendritic and somatic activity during REM sleep. This is particularly relevant in light of recent findings highlighting the role of REM sleep in synaptic plasticity (5). Further analysis will help us to better understand how dendritic activity is regulated across sleep states and by sleep specific oscillations.

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IS SLEEP A UNIVERSAL VITAL NEED? EVIDENCE TO THE CONTRARY IN DROSOPHILA MELANOGASTER

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Sleep appears to be a universally conserved phenomenon among the animal kingdom but whether this striking evolutionary conservation underlies a universally conserved vital function is still a very open question. Using novel technologies, we conducted a high-throughput, detailed analysis of sleep in the fruit fly Drosophila melanogaster and performed large scale experiments of chronic sleep restriction. Our results show that some wild type female flies are virtually sleepless in baseline conditions and that, contrary to expectations, complete sleep restriction is not a lethal treatment in Drosophila. Based on these results, we propose two new models for sleep function and conclude that, at the very least, a large component of sleep may not serve any strictly vital function.

NOTES

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