Part C1 - Project description, project title:

Interactions among hippocampal, thalamic and cortical networks in memory consolidation

Abstract

Sleep activity is crucial for consolidation of long-term memory. We can observe typical oscillatory electrical activity in the brain during deep sleep: slow waves and spindles in the thalamocortical system and sharp-wave ripples in the hippocampus. It was shown that coordination between these events plays an important role in the process of memory consolidation, but the mechanistic details are not understood. Because of current technology limitations, we do not have experimental recordings from larger enough number of neurons in parallel. The alternative is using computer models tuned by electrophysiological experiments, which allows us to explore the mechanistic details of the observed phenomena. We will develop advanced models of the neural circuity to explain coordination of key sleep oscillatory events, which lead to the transfer of memory between hippocampus and cortex. We will test, what factors are critical for coordination of the oscillatory events and how that coordination influences the transfer of synaptic memory traces, their stability and overall network capacity.

1 Current state of knowledge

The proposed project will study interaction of thalamo-cortico-hippocampal networks during sleep and its implications on the long-term memory consolidation by employing detailed biophysical models of sleep and plasticity. While there is no simple answer to the general function of sleep (Marshall and Born, 2007; Krueger et al., 2016), last decades of research clearly showed its fundamental role for consolidation of long-term memory – it may even turn out that memory consolidation is the main reason for the controlled loss of consciousness during (deep) sleep, since the brain shares similar neuronal circuitry for active information processing and its long-term storage (McClelland et al., 1995; Rasch and Born, 2013).

Different oscillatory patterns observed during sleep in EEG or intracortical recordings can be used to define specific sleep phases: REM (rapid eye movement) and non-REM (Steriade et al., 1993b; Lopes da Silva et al., 2005). The non-REM is further divided into N1, N2, N3 stages (Silber et al., 2007; Iber, 2007). Humans spend 75% of sleep in non-REM phase and specifically N3 phase of deep sleep shows slow oscillation (in range around0.7 Hz), during which Up and Down network states alternate (Aeschbach and Borbely, 1993; Steriade et al., 1993a; Chauvette et al., 2011). Those alternating states provide substrate for consolidation of (mostly declarative) memory (Hoffman et al., 2007).

Traditional model of consolidation is the 2-stage model (Buzsáki, 1989; Buzsáki, 2015). The first stage of this process occurs during the awake state. The neural circuitry (hippocampus is central part of it) quickly encodes and temporarily stores memory trace of current experience. The second stage occurs in sleep when, during replay, the temporarily stored traces in hippocampus are transferred to the neocortical networks, where the consolidation of long-term memory takes place.

The cornerstone of this two parts, hippocampal (new, labile traces) and cortical (old, stable traces) model of memory goes historically back to the description of famous retrograde amnesia case of patient H. M. This patient underwent surgery due to the otherwise untreatable epilepsy spreading across temporal brain areas. The operation induced lesions in hippocampus and parahippocampal temporal areas. After that he suddenly lost the ability of forming new memories, while maintaining the access to the old memories from his childhood (Scoville and Milner, 1957). Neuroscience has nowadays more complex understanding, how the hippocampo-cortical dialogue proceeds. First, there is ongoing debate to what extent hippocampus stores new memories, or whether it functions as an indexing service pointing to

memories already existing in neocortical sites. If the latter is the case, then consolidation process would include selection of replayed events in the circuit of hippocampus and not just simple memory transfer on the hippocampus-neocortex axis. Second, from the neurophysiological perspective, the following events (happening during N3 stage of sleep) play pivotal role: sharp-wave-ripple complex (SWR) in hippocampus, sleep spindles and transitions between Up/ Down-state (or around0.7 Hz slow oscillation in general) in neocortical sites (Bergmann and Staresina, 2017).

SWR is short (50 ms lasting) wave of neuronal hippocampal activity displaying in LFP (local field potential) as sharp-wave and associated ~ 150 Hz oscillation (Buzsáki, 2015; Joo and Frank, 2018), during which we can observe fast memory replay of recently experienced event (Foster, 2017). Within the same cycle of slow oscillation, which constitutes global time frame, this replay is synchronized with spindle oscillation in neocortex. Moreover, direct coupling to sequential replay in neocortical sites was observed (Ji and Wilson, 2007).

While it has been described that slow oscillation, spindles and sharp-wave ripples are critical for memory consolidation (Maingret et al., 2016), precise mechanism, how they are orchestrated, is not understood (Squire et al., 2015). Better understanding of the key events will be necessary first step for building memory prosthetic devices treating memory dysfunction (Ezzyat et al. 2018) and towards understanding long-term memory in general.

Current neurophysiology can record only limited number of neurons simultaneously, thus giving us only a glimpse at the actual neuronal dynamics. The viable option how to improve this limitation is to use mathematical modeling. Such models are convenient test bed for plausibility of proposed consolidation mechanisms as well as they also help to design and sift questions for forthcoming neurophysiological experiments (Postnova, 2019).

Our project is a continuation of experimental and modeling studies explaining mechanisms of plasticity (Skorheim et al., 2014; Volgushev et al., 2016; Sanda et al., 2017), sleep in general (Krishnan et al., 2016), slow oscillations (Timofeev et al., 2000; Bazhenov et al., 2002; Lemieux et al., 2014; Wei et al., 2016), sleep spindles (Bazhenov et al., 1999; Bazhenov et al., 2000; Fuentealba et al., 2005; Bonjean et al., 2011; Krishnan et al., 2018; Wei et al., 2018), sharp-wave ripples (Malerba et al., 2016; Malerba et al., 2017a; Malerba et al., 2017b; Malerba and Bazhenov, 2019) and last but not least recent pilot study of their coordination (Sanda et al., 2019) - at this moment first biophysical model including basic anatomical structures and key oscillatory events occurring at thalamo-cortico-hippocampal axis. Our goal is to use the pilot model to understand the dynamics of memory transfer between hippocampus and cortex and test the effect of spike timing jitter and noise on the interaction of thalamo-cortico-hippocampal networks.

2 Aims and Methods

2.1 Project relevance

How are memories created, recalled and sustained over longer period of time is one of the central questions of contemporary neuroscience. Basic structures and dynamic events associated with declarative memory have been already described, but the details of how individual structures and events interact together are unknown. Our project offers deeper understanding of these interactions and will formulate testable hypotheses, which could be independently tested in experimental labs. Existing mathematical models generally describe particular anatomical structures and detailing their events (e.g. SWR in hippocampus) or they describe many interacting structures without modeling phenomena on single neuronal level (e.g. mass models). What our pilot model provides is the combination two levels of description at the same time: high-level networks connecting key anatomical structures involved in systems-level events of consolidation and celular-level dynamics in which are formed individual memory traces. From the broader perspective detailed mechanistic understanding of the consilidation processes will also contribute to medical applications and development of new principles in artificial intelligence.

In the clinical setup we already see the coordinated efforts of developing memory prosthesis (DARPA

2013). which should help with memory recall (e.g. for the patients suffering traumatic brain injury). Such projects contain both experimental and theoretical part and it has been already shown that understanding personalized neural code significantly helped in the both short- and long-term memory performance (DARPA 2018a, Hampson et al., 2018). The proper functioning of memory consolidation mechanisms and memory reliance is dependent on the precise tuning of the individual oscillatory events, which were described in the previous sections of this proposal. We believe that ultimately the success of improved clinical interventions and devices will depend on the existence of accurate mathematical descriptions.

The second relevant area is artificial intelligence. Soon after the discovery of the concept of artificial neural networks, the scientific community encountered the problem of 'catastrophic forgetting' (French, 1999; McNaughton, 2010; Parisi et al., 2019). It has been shown that after designing the first neural network recalling a pattern, the attempt to learn the second pattern at a later time will either end unsuccessfully, or was at the cost of forgetting the first one. The dynamics of the Hopfield model, which we also intend to study, show the relationship of this phenomenon with the memory capacity limitations. Even after decades, this problem has not been satisfactorily solved. We know that nature has the solution, as brains or ganglia of lower or higher animal as humans, handle this task smoothly. The two-stage memory consolidation model described earlier is one promising way to help to solve this problem and allow neural networks of artificial intelligence to learn in a life-long manner (DARPA 2018b). Our recent work in this direction (Golden et. al 2020) shows how equipping spiking network with spontaneous replays during sleep-like period allows to overcome catastrophic forgetting when learning new decision making task.

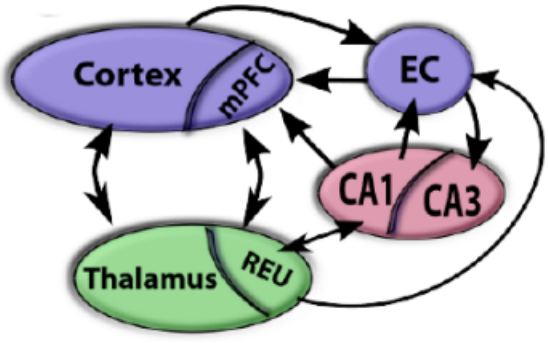
2.2 Project aims

The overall aim of the project is to understand the transfer of memory trace between hippocampus and neocortical sites and the dynamics of their interactions during the sleep activity. Our goals are in particular:

- Modeling plasticity and studying replay in hippocampal/ neocortical structures, transfer of memory trace and its stability across the learning periods.
- Estimation of memory capacity needed for robust memory storage.
- Modelling the interaction of key oscillatory events between individual anatomical structures.

2.3 Research objectives and methods

2.3.1 Structure of the model



We will use two types of models for simulating sleep dynamics: 1) Hodgkin-Huxley model of neurons for thalamo-cortical networks. The model will be an extension of the previous models (Bazhenov et al., 2002; Timofeev et al., 2000; Wei et al., 2016; Sanda et al., 2019), it will contain several thousands of neurons connected by AMPA, NMDA, GABA A, GABA B synapses and gap junctions. TC ('thalamic relay') and RE ('reticular thalamic') neurons of thalamus will use ion channels (INa, IK, ICaT, Ih) (Bazhenov et al., 1999; Bazhenov et al., 2000). Synaptic currents will be governed by equations described in (Timofeev et al., 2000; Houweling et al., 2002; Bazhenov et al., 2002). Neortical network will be modeled by single layer of neurons (layer 5), ratio between excitatory and inhibotory neurons will follow the experimental data (Thomson, 1997). In case that more detailed model of spindles is needed, we will use complex network containing several layers of cortex (Bonjean et al., 2011). Thalamic network consisting

of TC and RE neurons, in similar way as in (Bazhenov et al., 1998; Timofeev et al., 2000; Bazhenov et al., 2002; Sanda et al., 2019), will contain two types of TC neurons: "core" neurons forming focused projections (in case of multilayered model targeting layer 4 and 6) and "matrix" neurons diffusely projecting to neocortical network (layer 1 and 6 in multilayered case). The main targeted dynamics of thalamo-cortical network is slow oscillation with its transitions between Up- and Down-states together with spindles mainly occuring during Down-to-Up transition, as experimentally observed in N3 stage of NREM sleep (Wei et al., 2018).

2) Exponential leaky integrate-and-fire modek for hippocampal network (Malerba et al., 2016; Malerba and Bazhenov, 2019), which reduces computational load for densely connected part of the model. The network consits of two main blocks - CA3, where Sharp-waves originate and CA1, where ripples occur. Both subnetworks will contain population of excitatory and inhibityory (basket) neurons with dense connnectivity within the CA3 module and more sparsely connected CA1 region. Spontaneously (or thanks to the cortical input) activated subpopulation CA3 neurons triggers massive bursting in whole CA3 region (visible as a sharp-wave) and controlled by the of the recurrency in the circuitry. This wave of activation propagates to CA1, and evokes in turn high frequency oscillation event known as a ripple.

The global structure of the TC-CX-HP model is depicted on the figure above. The thalamus will be divided into nucleus reuniens and dorsal thalamic nuclei, neocortical network will contain mPFC (medial prefrontal cortex) which predomintly receives CA1 input. Apart from standard TC-CX connectivty nucleus reuniens will be conneted to CA1 (Çavdar et al., 2008; Varela et al., 2014).

3) For theoretical analysis we will use the Hopfield model of autoasociative memory (Hopfield, 1982). . The Hebb rule governing the synaptic plasticity in such networks can have a symmetrical formulation, written Wij = k Ri Rj, where Wij is the synaptic weight between neurons i and j, Ri and Rj are firing rates and k is a constant. There is not an uniquely prescribed algorithm, how to update the synaptic weights. The formula above also does not indicate, what time window is used. Nor it does say, whether and for what time interval is the memory formation delayed after activities of the pre- and post-synaptic neurons. The time asymmetry of the activities is the key to various Hebb rule modifications. Addition of the time delay between the two activities Wij = k Ri(t) Rj(t – Delta T) will enable storage of time sequences. This might be the background for forming procedural memory traces. We will attempt to transfer these observations into the reduced model. The next step of this transfer should be an explicit description of capacities of models with modified Hebb rules. The generation of the memory trace together with time delays (implemented based on the real axonal delays between the nuclei) will make possible to get an estimate of memory capacity (Wang et al., 2014).

2.3.2 Objective 1. Testing how hippocampal replay of action potentials improves strength of memory trace in neocortical sites.

We will use computational models simulating artificial awake training and and transfer of acquired memory during sleep consolidation activity and together with evaluation of neocortical recall performance. This allows us to connect the phenomena of sequential replay of neuronal activity with synaptic plastic changes improving memory trace in neocortex.

Hypotheses: a) Training of declarative memory task during the awake state leads to rapid reorganization of connectivity between hippocampal neurons.

b) During sleep hippocampus generates SWR, this way activating synapses, which were made stronger during training (and thus containing specific memory information).

c) SWR activation is projected from CA1 to neocortical site, where it supports cortical replay.

d) Spindles tune timing of action potentials in cortical neurons in such a way that spike-time dependent platicity (STDP) enhances specific cortico-cortical connections related to the consolidated memory trace.

Implementation: We will use the pilot model (Sanda et al., 2019) which will contain coordinated activity between SO-spindle-SWR events and enable STDP on synapses between HP-HP, CX-CX, HP-CX neurons. Including the plasticity will have an effect on the dynamics of the sleep oscillations and stability

of the replay. We will therefore need to spend some amount of time to tune separate networks (see section 3).

Training: After selecting replayed sequence of neurons in CA3 (this implies the sequence transfer to CA1), thus forming "memory trace", we artificially increase synaptic connections between the selected neurons. This will increase the probability of their correct reactivation during SWR. Alternatively, in more complex model, we will activate cortical neurons during training (and thus indirectly also the hippocampal neurons). After certain amount of repeated reactivations only HP-HP synapses related to the new task will be potentiated, unlike CX-CX synapses, which are less plastic.

Consolidation: During the coordinated oscillatory sleep events, cortical input triggers SWR in CA3-CA1 regions, which contain the memory trace. CA1->CX projections will transfer the SWR activation back to the neorcortical sites and influence the order of cortical firing during Upstates. We will test how activating STDP influence the ordering of cortical spikes.

Testing of Recall: We will stimulate only part of particular memory trace in order to test whether complete memory trace was reactivated.

This study follows up (Krishnan et al., 2016; Wei et al., 2016; Wei et al., 2018) and recently submitted pilot model by (Sanda et al, 2019). Using these results, we will be able to manipulate wakeful and sleep states in TC-CX network, measure synaptic activation, recall success or failure and touch exact timing of individual sleep segments and elements.

2.3.3 Objective 2. Testing critical elements involved in the process of memory consolidation

Hypothesis: Disturbance of sleep elements (SWR, SO, Down/Up transitions, spindles) or change in their relative timing causing the loss of synchrony will impair the consolidation and recall performance. Our models should identify the most critical mechanisms which dampen the consolidation process and suggest electrophysiological experiments to confirm their critical role.

Implementation: For the reduction (or complete elimination) of specific sleep elements we will specifically manipulate the model. Length and frequency of SO will be modulated by changing intrinsic currents, which will also time shift the transitions between Up and Down states. Experimental studies show coupling between SO, spindles and consolidation performance (Niknazar et al., 2015), thus we will manipulate timing difference between the events by introducing axonal delays between interacting anatomical areas. We also plan to test specific role of direct connections between hippocampal CA1 and nucleus reuniens (REU, thalamus) on synchronization, as it is known mediator of SO synchrony between neocortex and hippocampus (Hauer et al. 2019). It was experimentally shown that sensoric stimulation during specific phases of SO enhances memory consolidation (Wei et al. 2020) and we showed that exact hippocampal SWR timing within SO cycle highly affects spatiotemporal firing in targetted neocortical sites (Sanda et al. 2019). Thus and we will further study the effect of SWR phase on plasticity and consolidation in neocortex

2.3.4 Objective 3. Estimation of memory capacity

Hypothesis: There exist Lyapunov functions for the reduced model of memory, i.e. it is possible to find explicit function which predicts the memory capacity. Properly chosen construction of those functions will allow numerical and possibly analytical formulation of the capacity estimate.

Implementation: The reduced model has following advantage. Equations describing the reduced model can be derived from detailed model in a way enabling construction of simple invariants (in an ideal case by an analytical construction). More specifically, these invariants are Lyapunov functions enabling the memory capacity estimation.

Another property of memory trace is its stability. Stability can be studied in linearized system using its perturbations. Further on, the memory has a limited capacity, at least in models it can be filled up.

The existence of limits of memory model capacity was demonstrated by a classical result of J. Hopfield in his description of the Hopfield network. The capacity of the Hopfield network is limited. When

approximating the critical filling in of the memory model the memory starts to contain the spurious patterns (Parisi et al., 2019). (H. R. Wilson, 1999) in his book gives an explicit mathematical description of the invariants (besides others also Lyapunov functions) serving to memory capacity estimates. We will adapt his description as a general tool to study formation of memory patterns and to estimate memory capacity. Specifically, Lyapunov and other invariants will be constructed. We have preliminary analytical construction analogous to the BCM rule of changing synapse strengths (Bienenstock et al., 1982, Graupner and Brunel, 2018). Firstly we will approach the reduced model, because of its simpler dynamics and complexity. This should enable us to obtain the description of the linearized system derived from the reduced model.

3 Time schedule

3.1 2021-2022, Memory trace plasticity and stability

- Introduction of synaptic plasticity to individual parts of the model and studying stability of the synaptic memory traces in the context of sleep and its dynamics.
  - The developed model has to adhere to known oscillatory dynamics of the key events (SO/ spindles/ SWR) despite simultaneously ongoing plastic changes on the synapses of the neurons. Plasticity will be implemented via STDP (spike-time dependent plasticity) in similar way as it was modeled in (Sanda et al., 2017).
  - The model has to be able to create, or at least to retain new memory trace, which was artificially induced (e.g. by external stimulation of specific neurons).
  - The model has to be able to reactivate the traces in the form of sequential activation of specific neurons ('replay').

These features in turn allow:

- to obtain estimation of memory trace stability across longer time interval in the presence of sleep oscillations
- to test sequence replay and estimate the reliability of information transfer across hippocampal structures (CA3->CA1)
- to get tuned submodels needed in full model

3.2 2022 – 2023, Testing of memory transfer in the extended model

Testing of memory transfer between hippocampus and neocortex in the global tahlamo-cortico-hippocampal model equipped with plasticity and spontaneous reactivations, analysis of interactions between the different anatomical structures. The particular aims are:

- What is the robustness and mechanics of synaptic traces transfer on the CA1->neocortex pathway
- Stability/ consolidation of the memory trace in neocortex after the transfer
- Testing how critical are Down->Up, Up->Down transitions, spindles and SWRs for consolidation of the synaptic traces
- Testing the influence of perturbations of specific parts of the model events on the consolidation process
- Testing the influence of direct connections between thalamus (nucleus reuniens) and hippocampus (CA1) (we should have access to electrophysiological recordings stimulating thalamic sites)

- Testing the influence of connections from CA1->local inhibitory neurons in neorctical sites on the oscillation dynamics

3.3 2022 – 2023, Description of invariants in the reduced memory model

The reduced model will extract key dynamics in the memory trace storage cycle. Description of memory trace stability in the extended model will guide the description of the simplified dynamical system of the reduced model. This simplification will also make possible to estimate memory capacity.

Analytical and numerical estimates of memory capacity in a reduced model will use Lyapunov functions. Several aims of the reduced model study follow.

- To estimate, if and how gradual filling up of memory occurs and how it scales with the size of the neuronal circuitry.
- To identify, which parameters are characterising best the use up of memory capacity.
- To estimate, how the variantion of synaptic (and other) parameters influence the capacity.

4 International collaboration

This project will be developed in a collaboration with the lab of Maxim Bazhenov (UCSD, USA), who is world leading expert on memory and sleep modeling. During the span of last two decades he developed with experimental neurophysiologists (M. Steriade, I. Timofeev) biologically realistic models of sleep stages. The pilot model of hippocampo-thalamo-cortical circuitry have been already developed in our collaboration. We are also in contact with the lab of Eric Halgren (UCSD, USA) who is expert in recording and analysing human expertimental data we use for modelling. Tuning of the pilot model was also done by using experimental electrophysilogical recordings provided by Sydney Cash (Harvard Medical School, USA). In past we had access to data recorded in laboratories of A. Zador (Cold Spring Harbor Laboratory, NY, USA), N. Kopco (UPJS, Kosice, Slovakia), K. Jezek (Pilsen, Czech Republic) and others. We maintain relations to these laboratories.

5 Research team and facilities

The project will be coordinated by principal investigator Mgr. Pavel Sanda, PhD, who is currently researcher at the Institute of Computer Science, Czech Academy of Sciences. He was trained at the Department of Computational Neuroscience, Institute of Neurophysiology, Czech Academy of Sciences (description of olfactory and auditory pathways). Later he moved as a postdoctoral fellow for several years to the University of California (lab of Maxim Bazhenov) specializing on biologically realistic modeling of sensory pathways, neural circuits of sleep and plasticity.

Prof. Petr Marsalek, MSc, MD, PhD, will focus on the description of hippocampal memory trace formation and theoretical aspect of memory capacity. Prof. Marsalek spent two postdoctoral fellowships in the USA. From 1995 to 1997 he worked on detailed modeling of neocortical neural circuits in the laboratory of Christof Koch at the California Institute of Technology in Pasadena, CA. His second stay in the USA from 2000 to 2001 was at the Ernst Niebur laboratory of the Mind Brain Institute at the Johns Hopkins University in Baltimore, MD. As a PhD advisor he was mentoring project of J. Stroffek of studies of memory capacity in small neural circuits.

Dr. P. Šanda a prof. P. Maršálek have history of successfull cooperation, they have together described computational functional details of sound localizing neural circuit in the auditory brainstem and they continue to develop further understanding of this circuit.

For more challenging aspects of the modeling, the project will use parallel computing on a newly acquired linux cluster (12*160 cores) located at the Institute of Computer Science, Prague.

6 Expected results and project significance

Presented project addresses topic of crucial importance for human brain information processing. Despite current progress in design how artificial neural networks store and organize memory traces, our knowledge about analogical human brain data processing remains moot. Fundamental questions remain unanswered: How is maintained long term memory and is it necessary for the brain to spend significant part of time in unconscious sleep to secure such function? How can be high capacity of mammalian memory maintained, repaired and even improved? Can we use those mechanisms for attaninng life-long learning in artificial machines? How can this expertise contribute to existing attempts to strengthen memory using electrical stimulation devices? We aim to study intricacies of what are underlying neural processes of human thalamical, cortical and hippocampal interactions in building up, maintaining and organizing memory traces in life long memories and sleep wake cycles. We will compare our predictions with the data obtained in human intracranial recording. The project will be using and further developing the best state-of-the art computer models for simulating the critical events known to play role in this dynamics. The results will be published in at least 3 impacted papers.

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