Neuromodulation of synaptic plasticity rules avoids homeostatic reset of synaptic weights during switches in brain states

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Summary

Brain information processing is shaped by fluctuations in neuronal rhythmic activities, each defining distinctive brain states. Switches in brain states during wake-sleep cycle are described at the network level, by a neuronal population shift from active to oscillatory state. At the cellular level, neurons *switch from tonic to burst*. This switch is organized thanks to *neuromodulators*. They refer to signaling molecules that induce reversible changes in functional properties of neurons or synapses. Simultaneously, learning and memory are attributed to the ability of neurons to modify their connections based on experience, a property called *synaptic plasticity*. It exploits the correlation level in the activity of connected neurons. Altogether, sleep contributes to memory, a phenomenon called sleep-dependent memory consolidation. Experimental results show a down-selection mechanism i.e., strong (resp. weak) connections established during wakefulness are preserved (resp. decreased) during sleep. However, little is known about its underlying physiological processes. This research leads the way to uncover biological explanations.

Using a conductance-based model robust to neuromodulation and synaptic plasticity, we built a cortical network to study the evolution of synaptic weights during switches in brain states. We tested several types of synaptic plasticity rules such as triplet and calcium-dependent models. We reproduced experimental data acquired in wakefulness. Then, switching the network from tonic to burst without any modification of the synaptic rule leads to a *homeostatic reset*. All synaptic weights converge towards the same basal value whatever the rule due to neuromodulation of neuronal activity.

We showed that neuromodulation of synaptic rules is necessary to overcome this reset. For triplet models, the spike-time dependent curve is deformed as demonstrated in [Gonzalez-Ruedas,2018]. For calcium-based models, calcium thresholds are neuromodulated or the potentiation level is weight-dependent due to neuromodulatory markers. The neuromodulated-synaptic rules are shown to support the down-selection mechanism during sleep, avoiding the homeostatic reset.

Switch from tonic to burst activity leads to a homeostatic reset of synaptic weights following classical triplet or calcium-based synaptic plasticity rules

To explore the interaction between switches in firing activity and synaptic plasticity in the context of sleep-dependent memory consolidation, we proceeded step by step. (A) We built a cortical network that reproduces the activity during different brain states as established in [McCormick,1998; Zagha,2014].

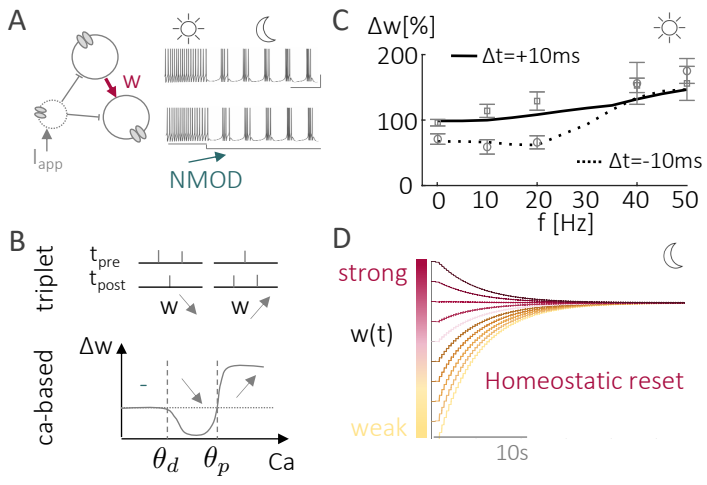

Figure 1. A. Cortical network composed of conductance-based models. The inhibitory neuron (dotted circle) projects to two excitatory neurons. The hyperpolarizing current switches the membrane voltage (traces) from tonic to burst by reproducing the effect of neuromodulators (NMOD) (scale horizontal line=0.5s and vertical line=50mV). Plasticity is implemented at the connection between the two excitatory neurons (red arrow). **B.** Synaptic plasticity rules. **C.** The different synaptic rules are fitted to reproduce the firing-rate dependency in a pairing protocol [Sjostrom,2001: circles=+10ms, square=-10ms]. **D.** Evolution of the synaptic weight w(t) during bursting activity. Switch to burst generates a homeostatic reset whatever the synaptic plasticity rule.

Our cortical network is composed of an inhibitory neuron projecting GABA currents on two excitatory neurons connected by an AMPA current. Each neuron is a conductance-based model proved to be robust to neuromodulation and synaptic plasticity [Drion,2018; Jacquerie,2021]. Applying a hyperpolarizing current, which models the effect of neuromodulators, switches the network from tonic to burst (Fig.1A). (B) We integrated synaptic plasticity between the excitatory neurons. We implemented two categories of plasticity rules to compare their behaviors during switches from tonic to burst. The first category comprises phenomenological models such as the triplet model using pre-post-pre or post-pre-post spiking activity to change the synaptic weight [Pfister,2016; Graupner,2016]. The second category comprises biological models using calcium as the key signal. Synaptic potentiation or depression is activated when calcium crosses distinct thresholds (θ_d, θ_p). High (resp. intermediate) calcium levels cause a fast strengthening (resp. slow reduction) of the synaptic weight called potentiation (resp. depression) [Shouval,2002; Graupner,2012] (Fig.1B). (C) We validated the model on experimental data acquired during wakefulness. The model reproduces the results on rate-dependent plasticity in pairing recordings [Sjostrom,2001] (Fig.1C). (D) We compared strong and weak initial weights acquired during wakefulness characterized by the exogenous tonic activity. Then, the network switches in bursting mode, an endogenous firing activity associated to sleep. It results in a *homeostatic reset* meaning that whatever the strength established during wakefulness, the network resets its connectivity to a steady-state value for both triplet and calcium-based models. It is explained by the role of calcium in homeostasis; switches in firing pattern are associated with a change in calcium dynamics generating homeostatic processes (Fig.1D). The results suggest that maintaining a learning rule compatible with wakefulness behavior cannot explain sleep-dependent memory consolidation mechanisms.

Neuromodulation of synaptic rules overcomes the homeostatic reset

Recent evidence shows that synaptic plasticity rules are also under the control of neuromodulators by e.g., acetylcholine, dopamine, noradrenaline, serotonin, and histamine [Brzosko,2019]. In the context of sleep-dependent memory consolidation, [Gonzalez-Ruedas,2018] demonstrated the preservation (resp. decrease) of strong (resp. weak) weights is feasible by using a state-dependent synaptic rule (Fig.2A-top). Indeed, the classical depression-potentiation kernel in wakefulness is deformed into a depression kernel in sleep (Fig.2B-top) (similar work is done in [Pedrosa,2017]). We reproduced this experience with the triplet models as illustrated by the time-evolution of synaptic weights (Fig.2A-bottom). However, it lacks biological interpretation. Therefore, we explored different neuromodulatory effects on calcium-based models to reproduce the down-selection process. (i) We showed that the depression and potentiation thresholds are good targets for neuromodulation-induced changes (Fig.2C-top). (ii) Another target is the weight-dependency of the potentiation level that is consistent with the synaptic tagging-and-capture hypothesis [Gerstner,2018]. Overall, our model helps to uncover functional and biological mechanisms governing sleep-dependent memory consolidation. It can be easily extended to a large cortical network to study memory engram. For experimentalists, it is a powerful tool to target neuromodulation-induced plasticity processes.

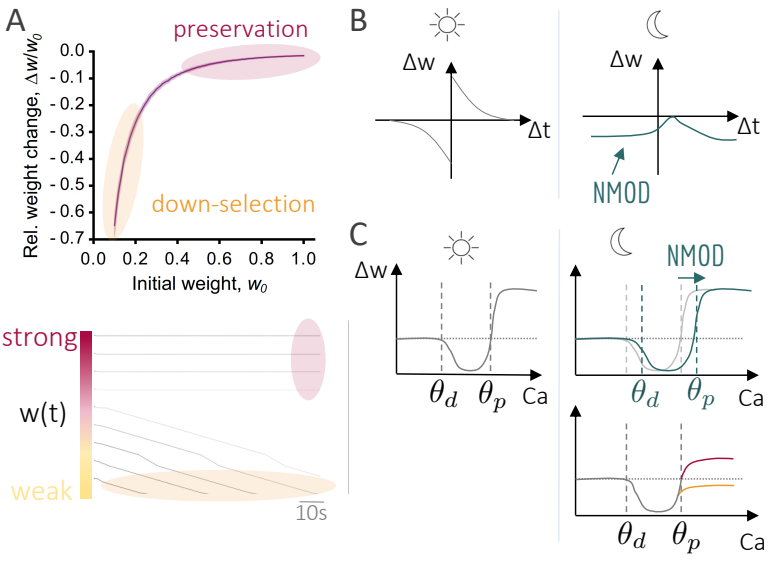

Figure 2. A. (top) Down-selection process from [Gonzalez-Ruedas,2018]. (bottom) The associated time-evolution of the synaptic weights. Strong (resp. weak) weights are preserved (resp. depressed). This behavior is reproduced by our neuromodulated-synaptic rules described in (B-C). **B.** Spike-time dependent function of the triplet model is deformed under neuromodulators (NMOD). **C.** Calcium thresholds are shifted under neuromodulators (top) and potential levels are weight-dependent (bottom). These changes in the calcium-dependent models avoid the homeostatic reset and reproduce the down-selection process.