



HAL
open science

A functional model of memory-oriented cooperation between hippocampal and cortical regions across sleep-wake cycles

Dominique G Bérroule

► **To cite this version:**

Dominique G Bérroule. A functional model of memory-oriented cooperation between hippocampal and cortical regions across sleep-wake cycles. 2023. hal-04292391

HAL Id: hal-04292391

<https://hal.science/hal-04292391v1>

Preprint submitted on 17 Nov 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

A functional model of memory-oriented cooperation between hippocampal and cortical regions across sleep-wake cycles

Dominique G. Bérroule

Keywords: Learning, phase coding, place coding, neuromodulation, neurogenesis, axonal sprouting, ionic signalling, cortical columns.

Article type: Hypothesis and Theory

Abstract

Whereas usually deemed to be mediated by *synaptic plasticity*, the formation of long-term memory may rely on *dormant immature neurons* distributed over the cortex, especially in mammals with large brain. Notably owing to axonal sprouting, these precursors of cortical cells could be engaged with subcortical *neurogenesis* into the brain lifelong adaptation to changing environment. On the computational modelling side, *Guided Propagation* memory models implement coincidence-detectors that are dynamically recruited for the experience-driven growth of long-lasting memory paths. The latter are meant to integrate/generate trajectories of discrete events at the basis of sequential learning and behaviour, known as a cortical function (*Cx*). To account as well for short-term memory, renewable phase-coding is supported by generic paths whereby serial patterns can instantly be retained and replayed (likely a hippocampal function: *Hp*). When repeatedly broadcasted through inner modulation signals during a suitable anticipation-free state, namely offline, every such trajectory recorded by *Hp* may give rise – via the Thalamus - to permanent traces encoded within *Cx* channels, provided unused coincidence-detectors at disposal. Conversely, cross-links built between parallel channels notably guide the learning of embedded trajectories, and allow *Cx* to inform *Hp* about their novelty in order for *Hp* to record unexpected events. Potential neural contributors to learning are addressed here from this collaborative perspective, including hippocampal and cortical replay, electric oscillations and transients, monoaminergic and ionic signalling. Computer experiments show how phasic/tonic and activation/modulation signals can together support the translation of *Hp* temporary characteristic phases into *Cx* memory maps over series of simulated online/offline cycles. By projecting the causal relationships linking the model components onto neurobiological data, predictions are made about processes which underlie learning and memory. The issue of whether quiescent cortical cells in reserve could be embedded in the working cortex in due course is eventually investigated in the light of recent molecular and anatomical insights, which elicits a functional matching between the proposed architecture and Hippo-thalamo-cortical circuits. There thus emerges a form of lifelong brain development wherein thalamic waves accompanying the hippocampus offline reactivation of previous online experience coincide with cortical spontaneous activity so as to grow cortical maps which combine existing and free canonical circuits.

1 Introduction

While the interplay of cortical and subcortical structures (e.g. the *Hippocampus* HP) is known to guide memory retrieval (Preston & Eichenbaum, 2013), the study reported here rather focused on the collaborative contribution to memory encoding of selected brain structures, including neocortex and HP. Conversely, this central topic had to be extended to peripheral notions, including in first place the neural representations that are targeted by the joint action of distinct brain regions.

For as far back as neurobiological studies concern learning and memory, the *potentiation/depression* of synapses - that translates to the enhancement/inhibition of signal transmission between neurons (Bliss and Gardner-Medwin, 1973; Markram, 1997) - is reckoned to hold a key position for information storage in the brain. Memory formation can in particular be affected by pharmacological and molecular manipulations of factors that control *synaptic plasticity* (Mondadori et al, 1989; Newcomer et al, 2000). Protein-dependent consolidation has however been questioned by neuroscientists who noticed that the synthesis of proteins is neither specific to learning situations nor necessary to memory storage, while forgetting is quickly reversible, hence likely not caused by changes in synaptic plasticity (Gisquet and Riccio, 2018). At odds with these arguments but in line with an historical and sustained focus on the consolidation model, Artificial Neural Networks (ANNs) implement a preliminary training stage meant to gradually update weighted connections within a fixed matrix of formal neurons (Le Cun, 1988). But still, the dynamic and context-dependent adaptation of the brain to unforeseeable environmental variations cannot properly be explained by this only ‘connectionist’ approach which, by the way, does not require the collaboration of distinct networks like the brain does. Other experience-driven modifications of the neural substrate than synaptic ones are thus worth considering. Coincidentally, advancing knowledge elicited from *adult neurogenesis* (Altman, 1962; Colangelo & al., 2019) may induce designers of biology-motivated models to overstep the only controlled fitting and pruning of synaptic shrubs, in keeping with the broader concept of *neural plasticity*. Topical modelling attempts may even depict instances of “neural network expansion” suitable for knowledge to be stored and maintained over both short- and long-term timescales with a twofold intention: contributing to the aforementioned ‘dynamic adaptation’ issue, and preventing impeded access to previously stored data as illustrated by the *stability-plasticity dilemma* (Abraham and Robins, 2005). First referred to as ‘*catastrophic interference*’ (McCloskey and Cohen, 1989) in the shared hardware of ANNs (Chen & Liu, 2018), this phenomenon pertains to the ANNs trend for recent information to take the lead over older one, despite the rebalancing of all synaptic weights postulated to occur overnight (Tadros, 2022). Not often mentioned, synapses likely undergo transient neuromodulating signals, a phenomenon that would also affect knowledge if it were only coded in connections strengths. For one thing put forward here, the dynamic assignment of add-on units to ‘private locations’ engram avoids degradation of previous acquirement. Eventually, for Long-Term Memory (LTM) to be updated without impairing the current storage, supplementary units could be recruited *in situ*, be they issued either prior or after birth from a neurogenic niche.

Based on these premises, the functional memory model presented here implements the instant recording of events (Short-Term Memory, STM) by assigning them distinct characteristic signals ahead of their translation into persistent memory traces. The ordered and recurring activation of the same signals (i.e.: replay) allows the gradual growth of these traces when circumstances are favourable. Whether both molecular mechanisms and neural structures can actually support this

dynamic building of LTM from STM replay in a timely manner will eventually be addressed, disclosing the model mapping onto thalamocortical circuits and hippocampus.

I.1 Neurogenesis and axonal sprouting beyond injury repair

Biological data relevant to the development of mammalian adult brains not only include *hippocampal* and *striatal* neurogenesis (Jurkowski et al., 2020), but also the proliferation of neural cells along the forebrain *lateral ventricle* towards the *olfactory bulb* (Morshead et al., 1994; Gonzalez-Perez, 2012). In humans, evidence for experience-dependent variations of cortical structures comes from *magnetic resonance imaging* during periods of extensive learning. Whereas measured variations in the blood flow basically reflect the ongoing neural activity, they are also usually considered as signs of «gray matter increase» (Draganski et al., 2006) and «volume changes» (Wenger et al., 2017) consistent with neurogenesis. It may, however, be observed that territories supplied with blood would also extend if quiescent circuits were called to serve LTM, provided their balanced distribution over the cortex. Indeed, large populations of immature neurons with a prenatal origin have been discovered within cortical layer 2 (Bonfanti and Nacher, 2012), allowing the adult neocortex of large mammals to let in a reservoir of cells (König et al., 2016; La Rosa et al., 2020) so as to “*maintain cognitive processes throughout life*” (Kempermann, 2020). As a matter of assumption, the availability of add-on cells in both sub-cortical and cortical regions is mostly deemed beneficial in the event of either stroke or degenerative diseases (Fuchs and Flügge, 2014; Ohira, 2018). Nonetheless, the intervention of new neurons does not seem essential in response to brain damage, for the latter may be reduced by *glial cells* already in place: *Astrocytes* reprogramming can currently be obtained in vitro (Kuangpin et al., 2020), supported by certain pools of *microglia* (Pérez-Rodríguez, 2021) under specific *transcriptional factors* (Liu et al., 2020). Without overlooking their remedial power, free *Neural Stem Cells* (NSCs) could also be assigned a key function in memory processes. More precisely, the enduring storage of new information may primarily rely on the incorporation of free processing units prone to extend their *neurites* (i.e.: axons, dendrites) into an evolving circuitry, rather than on the updating of pre-existing connections. Neurites sprouting ahead of synaptic formation would afterwards be sensitive to molecular manipulations, in line with the wealth of experience accumulated over years on the memory consolidation matter. In this developmental perspective, how and when neurites could be steered towards proper targets appears to be central.

I.2 Different brain regions for complementary memories

Despite potential advantages mentioned above, the “add-on units” encoding assumption lays a heavy burden on the information storage part, especially when real-time performance is expected, as for STM. If layer-2 dormant NSCs were to be involved in human STM, they should be awakened and matured before their neurites are guided towards some destination. Although the recruitment of nearby near-neurons would significantly shorten the whole process as compared to the migration of rodent NSCs from remote subcortical niches (Lois and Alvarez-Buylla, 1994), the immediate storage and retrieval of novel information remains elusive in this way.

A solution to this strong temporal constraint may be provided by the hippocampus. This brain device has indeed “*the capacity for encoding novel episodes throughout life, many of which cannot be anticipated a priori*” (Aimone, 2016), and several clues indicate that episodic events are first preserved there in a format allowing their immediate recall until more sustainable storage can

be carried out within the cortex. This encoding issue is to be addressed here without neglecting the contribution of neurogenesis: Amazingly enough, around 250,000 new neurons likely support encoding by being incorporated in the HP *subgranular zone* of rodent brain, from the survival of one third of those mostly produced overnight (López-Virgen et al., 2015). The existence of persistent adult neurogenesis is however more controversial in humans' subcortical regions. In the *striatum*, the regular incoming of newborn cells may “*serve to maintain a pool of neurons with unique properties, present for a limited time after birth*” (Ernst et al, 2014). Found to decline significantly after one year and across childhood in the HP *dentate gyrus* (Sorrells et al., 2018), neurogenesis might however be handed over to another substructure (Nogueira & al., 2018). In any case, how the human hippocampus could support STM without relying on whole-life neurogenesis can now be considered with a memory model formerly applied to LTM.

I.3 A functional model for studying interactions between memory modules

On the modelling side, the multi-storey and multi-channel *Guided Propagation* (GP) systems accommodate the growth of memory paths for learning time-space patterns of sparse activity (Bérroule, 1989). The lack of interference between already stored and new representations – as wanted by ANNs - results from a dynamic and incremental type of learning which assigns new private locations to new situations (i.e.: novel context-stimuli coincidence). Although the GP algorithms whereby inner references develop in the course of processing have been explored for different tasks (Bérroule, 2004), including problem solving (Blanchet, 1994) and neurobiological modelling (Toffano et al, 1994, Bérroule and Gisquet-Verrier, 2016), to design a GP system with fast, physiology-compatible STM had not been envisaged before the work reported here. A main format of storage – so-called *topological* – was used in most applications with apparent swiftness only due to computers ability to instantly link and manipulate objects (See: Supplementary File). Subsequently, elements of sleep research got involved in this puzzling gap between immediate and persistent memory, for it became clear that offline periods were required for a topology of memory paths to properly settle down. Bearing in mind the coding dimensions potentially available to systems with ‘information holding’ capacity, the GP approach can be turned closer to biological timings. In that respect, facts and hypotheses relating neurogenesis, memory and sleep will be reported after a reminder of computationally tractable codes. The updated GP model introduced afterwards will concentrate on the issue of immediate information retention through temporal coding (i.e.: binding with shared phases), as well as how this temporary encoding can be transformed into LTM, provided proper neuromodulation. With its ability to convey both neuromodulating and activation/inhibition signals, this computational tool revealed suitable for testing how the HP, serving as a substrate for short-term memory, may interact with cortical regions supporting long-term memory, at the pace of sleep/wake cycles. Generated by computer simulations, activity histograms of increasing sophistication will witness the signalling that accompanies memory storage and recall across a multiple-replay scenario aimed at long-lasting memory.

2. Memory encoding across sleep and wakefulness

Whatever the world maps that are formed in the brain, the underlying mechanisms are likely influenced by sleep-wake cycles. Alternations of complementary online and offline states can thus be argued to condition the accuracy of information storage further than the beneficial global effects on memory usually attributed to sleep (e.g.: the SHY model, Tononi and Cirelli, 2014).

2.1 Birth, migration and maturation of neurons throughout life

The genesis of neurons precedes their possible migration, followed sooner or (much) later by their neurite's extension and connection to the existing circuitry. This “neurofarming” storyline may be regarded as accompanying the brain development along a lifespan.

2.1.1 Complementary codes for information processing

Information encoding relies on the same basic dimensions in ways that depend on the host memory substrate. In computers, it is mainly contained in ‘registers’, while temporal information (e.g.: access-time to registers) cannot be meaningful for architectural reasons. By contrast, time seems to hold a prevailing part in the brain whose online activity is locked to the timing of environmental stimuli. Spatial positions are significant as well, generalizing the former disclosure of *place cells* in the HP (O’Keefe and Dostrovsky, 1971). Of note, although neural representations of a given event are often viewed as distributed over large networks, their sparsity is increasingly evidenced by experimental results (Tonegawa et al., 2015; Han et al, 2021). Putting it all together, and consistently with the “local view” implemented in GP systems, both time and space participate in *sparse coding* whereby an event is coded by the strong selective activation of a few neurons over a limited period of time (Erwin et al, 2020).

Whereas the average rate of spiking activity approximates the strength of stimuli/actions, neural signalling is also believed to convey more specific information through its micro temporal organization. Evidence of fast visual identification of scenes notably lends support to a form of neural coding in which the temporal coincidence of pulses across a population is more informative than their rate averaged over time (Van Rullen et al, 2005). This is through the position of a periodic spike/burst within a given time interval, namely its *phase*, that the components of a given event can thus distinctively be bound. Neurons temporarily sharing such a characteristic phase are “grouped into a hierarchy of patterns in a flexible way, without the introduction of new hardware for new patterns” (Von der Malsburgh, 1981, 1999; Singer, 1999). In support of this set-up, waves of spikes with different phases have been found which cohabit and code respectively for different objects or variables (Lisman & Idiart, 1995). A baseline signal, common to several brain regions - not necessarily showing sustained rhythmicity (Bush & Burgess, 2019) -, provides the reference ‘phasic interval’ within which a shared phase can be meaningful. For instance, the phase to which cells of rodent HP are locked becomes shorter (*precession*) as the receptive field is traversed (Hafting et al, 2008) across daily trials, which suggests a possible dynamic management of phase coding associated with ‘episodic cells’ (Hasselmo, 2005). Neuronal spikes generated in several cortical areas can indeed be phase-locked to the HP *theta* rhythm (4-8 Hz), known as the most regular slow EEG oscillations (Nuñez & Buño, 2021). Accordingly, a common cyclic spiking time binds sensorimotor elements stemming from different brain regions so as to form an episodic memory: In humans, recalls deteriorate when different sensory channels (visual, auditory) are not properly synchronized (Clouter et al., 2017). Relevant theta oscillations also occur during sleep, with a trend to synchronize *paradoxical sleep* (PS) through short bursts (Cantero et al, 2003). Regardless of the broad range of oscillations frequencies, their phase is shared throughout HP (Zhang and Jacobs, 2015), and even wide fluctuations of the baseline frequency, as observed in bats (Bush and Burgess, 2019) may not impede tuning to theta-range (Marrosu, 1994). In addition, each theta cycle can host bursts of the faster *gamma* rhythm (40-80 Hz) at distinct temporal positions (Hakim and Vodel, 2018), thus providing another phasic information embedded in the theta rhythm.

To sum up this short review of neural coding, distinct signalling dynamics underlie the so-called *engram* whereby synchronization between short pulses (i.e.: spikes, bursts) can temporarily bind the involved cells (fine-grain time-coding), while the relative order of their respective activations could match series of stimuli (*temporal topology*). Besides, the relative positions of engram cells can also be meaningful by forming a *spatial topology*. As far as learning is concerned, none of the above types of coding is easy to handle. First, mobile spike trains cannot compare to computer static ciphers well-suited for storage and loading procedures. Second, with respect to the temporal dimension, the synchrony constraint must be satisfied between inner and sensory signals often impacted by non-expectable variations and noise. Third, brain spatial locations cannot straightforwardly be allotted, given their interdependencies that presumably reflect those between the world events they stand for. When facing this riddle, a global solution is however worth seeking that would incorporate every aforementioned dimension, namely *time*, *place*, and *content*, the latter taking the form of periodic pulses synchronized across elements of the same pattern.

2.1.2 Place coding and adult neurofarming

The availability of a stand-by population of potential place-cells is seen here as a facility for setting up the foregoing strategy, especially for composing topological maps wherein events are represented by *relative time-space locations*. As far as biology is concerned, specific HP place-cells have been observed to bridge events by activating their respective representations in order (Eichenbaum, 2013; Taxis, 2015), including during sleep (Lee & Wilson, 2002). On the experimental side, as a rodent is running along a track, with each of its HP neuron's activity selectively tuned to one track location, a temporal sequence of firing is induced in place-cells, including their fast firing in the right order prior to a run, and in the reverse order after-run (Diba and Buzsáki, 2007; Buhry et al., 2011). Advanced proposals concern the modulation of HP function whereby newborn neurons would act as novelty detectors and “*promote the separation of memory indexes by increasing the sparsity of neural representations*” (Berdugo-Vera et al, 2021). But in fact, the HP activity is so sparse, being estimated to 1-2% of the principal neurons (*dentate granule cells*) total population (Wang et al., 2020), that some authors wondered “*why a predominantly silent network would need to continually incorporate more functional units*” (Piatti et al, 2013) presumably associated with enhanced synaptic plasticity (Schmidt-Hieber et al., 2004). This thought clearly reflects the disbelief that acquiring new knowledge could rely on add-on units. Indeed, when associated with fine-grain time coding, place-coding does not appear so dependent upon new units at disposal, as long as distinct characteristic phases are available. Furthermore, and as previously highlighted, the putative involvement of free neurons in the quick formation of localized memories is challenged by their time-consuming motion and maturation until they land eventually at proper locations. This limitation applies unless neural cells are already both adequately located and fairly mature.

2.1.3 Reduction of the migration load before maturation

Recent decades have witnessed a change in perspective with respect to the only repairing object of adult neuroplasticity, especially since the report that a complex sensorimotor behaviour (i.e.: song learning in canary) involves new neurons for building relevant circuits (Nottebohm, 1989). However, despite evidence of post-natal neurogenesis in the HP of several species, approximating the age of neurons marked by *Carbon 14* put a halt to expecting similar processes in the human cortex. Actually, among post-mortem neurons that were born at different times across a lifespan, none was found in the neocortex, demonstrating that “*whereas non-neuronal cells turn over, neurons in the human cerebral neocortex are not generated in adulthood at detectable levels but*

are generated perinatally” (Bhardwaj et al, 2006). Other birth-dating analyses have confirmed a verdict that dismisses the dynamic incorporation of recently born neurons into cortical networks of human beings (Llorens-Martin and Trejo, 2011). But then, what about revisiting the dogma that stated “a fixed number of neurons at birth”? Among cells born before birth, some apparently head for cortical regions without serving the developing brain. Years and even decades after, these perennial adolescent neurons in ‘stand-by’ state could complete their growth by adopting traits which meet architectural needs at that time. In agreement with this view, cells which express the *doublecortin* (DCX+) marker of immaturity have been uncovered in adult primates (Zhang et al, 2009), forming a potential reservoir of “aspiring neurons”. These potential add-on units are located in the aforementioned layer 2 of the cortex. Regarding the size of this reserve in relation with those of several mammals’ brains, estimations give more than 2 million DCX+ cells in chimpanzees, as compared to one hundred in bats and none in mice (La Rosa et al, 2020). During their evolution, in parallel with neurogenic subcortical niches, certain species would thus have developed the prenatal skill of building up cortical reserves of neural precursors through pre-natal migration. In short, largest brains implement *quasi in-situ* near-neurons, whereas the migration of NSCs from niches would otherwise be prioritized.

In any case, migration and axonal sprouting likely share steering principles that are worth considering here. In order to proceed towards experience-driven targets (Devreotes and Horwitz, 2015), NSCs undergo attractors and repellants influences, including from the Ca^{2+} calcium ion (D’Arcangelo, 2014) whose increase is notably known to lower the excitability of neurons. Once migration is completed, dendrites expand concurrently with synapses genesis: “*neuronal migration is largely incompatible with other programs of differentiation because this latter process drives cells into the acquisition of morphological features that are unsuited for migration.*” (Marin et al., 2010). This statement raises a rational expectation linking sleep/wake alternation to neurofarming, namely a system of rotation between motility and rising of specific morphologies. This hypothesis is reinforced when bringing two recent research outcomes together. On one side, major changes of brain state could be mediated by ionic currents, including in particular the $[\text{Ca}^{2+}]_e$ interstitial concentration of calcium ion which was found to determine either arousal (low level) or falling asleep (high level) (Landolt and Holst, 2016; Rasmussen et al, 2020). On the other side, NSCs’ migration would be maintained by low levels of Ca^{2+} , until increased transients inhibit their slow crawling motion on arriving at the sites where they mature (Medvedeva & Pierani, 2020), select proper dendritic spines (Li et al., 2017), and are incorporated in the local network (Toth & al, 2016). This correlation between cyclic variations of $[\text{Ca}^{2+}]_e$ and sleep/wake alternations underpins the part played by brain states in the lifelong association between neural genesis, motility, maturation and connection to operative circuits (i.e.: neurofarming). Already observed instances of sleep-related modification of the neural tissue are however scarce, apart from synaptic bouton expansion in *drosophila* (Singh et al., 2010) and specific formation of dendritic spines (Yang et al., 2015). The offline status is at least thought to favour the upgrading of synaptic strength and spine density underlying engram, the problem of neuronal allocation set aside (Josselyn and Tonegawa, 2020). Although the learning-driven integration of NSCs in the adult cortex lacks evidence at the physiological level, this eventuality may benefit from additional knowledge on sleep.

2.2 Hippo-cortical interactions paced by sleep/wake cycles

Sleep is far too time- and energy- consuming a brain state for being reduced to its only recovering function. It is notably recognized as beneficial to memory, owing to its associated sensory disconnection. But still, one may admit that proper memorization can be prevented from

the potential threat of environmental stimuli without appeal to more than six hours of nightly retreat. More convincing reasons must therefore be promoted to explain why every animal with a brain is periodically lost in deeper and deeper unconscious states despite survival hazards in a world filled with predators. When referred to as an ‘offline period’, sleep is indeed considered a time of reduced intrusion of external stimuli (Barnes and Wilson, 2014), whereas stimuli internally produced by the brain are seldom mentioned as a source of “contextual interference” in memory-oriented justifications of sleep (Yonelinas et al., 2019). Notwithstanding extensive research on brain circuits that control sleep (Watson et al, 2010; Brown et al, 2012), how exactly these circuits are modulated by environmental factors, including prior events liable to learning, remains unclear. The resulting structure of sleep is nevertheless well specified. Electroencephalograms (EEGs) first evidenced short high-frequency waves transiently superimposed with deep oscillations occurring across cyclic stages that form the ‘sleep architecture’. Overnight in human, healthy rest is composed of five cycles in average, lasting about 90 minutes each. One cycle goes from light to deeper and deeper Slow-Wave Sleep (SWS) before switching to the intriguing paradoxical sleep (PS) during which rapid eyes movements (REM) witness an awake-like brain activity associated with vivid dreaming (Mutz and Javadi, 2016). “*REM sleep may facilitate schema disintegration due to its highly associative nature*”, which likely promotes creativity (Whitehurst et al., 2016). Free of interfering stimuli, this well-orchestrated plot is believed to contribute to LTM (Rasch and Born, 2013). To sum up, one may acknowledge that sleep provides an opportunity to re-utter and process previously recorded events without disturbance not only caused by environmental stimuli, but also by inner signals strongly streaming across regions of the awake cortex.

2.2.1 Transient waves underlie the replay function

In the beginning were spontaneous oscillations, followed by sensory events replay, both phenomena evidencing the prevalence of inner activity in brain functions (of note, spontaneous activity is also indispensable in the GP systems to be featured in the next main section). Multiple replay of sensory input already occurs during the first postnatal week, under a *thalamic oscillator* (Minlebaev et al., 2011) serving the development of *cortical columns*, an “*elementary unit of organization*” repeated iteratively across every brain area (Mountcastle, 1957; 1997). The *thalamus* indeed plays a critical role in the integration of sensory events and their dispatching towards other brain regions. A sort of sensory switch occurs after birth as spontaneous local and dense bursts in the sense organs are replaced by more continuous activity undergoing wake/sleep alternation (Colonesse and Phillips, 2018). This is in this context of changing level of consciousness that spontaneous rhythmic activities, internally driven replay of activity patterns, as well as reservoirs of near-neurons likely participate in learning.

During sleep, sequential patterns are repeatedly replayed in order, which may differ from either forward or backward replay found in the waking state of rodents (Buzsáki and Lopes da Silva, 2012). Direct evidence of learning-related replay has also been uncovered in the human brain (Eichenlaub et al., 2020, Findlay et al, 2020), in line with the finding that neural populations firing peaks while awake fit those of the following sleep. Provided that the same sequence occurs often enough, and that the same sensorimotor behaviour can be rehearsed, conscious training also stays “*under the replay banner*” (Findlay et al, 2020), whereas multiple overnight (unconscious) replays seem mandatory in the case of a single experience unless it is strongly emotional. Turning now to neural signals that underlie replay is intended for preparing the subsequent presentation of possible interactions between GP channels, namely *Hp* and *Cx* that respectively represent subfunctions of HP and a cortical channel.

2.2.2 Joined activities of cortex and hippocampus

Intra-cortical studies have emphasized distinct propagation phenomena that mediate interactions between cortical areas and limbic structures of the human brain, including HP and Thalamus. Neocortical slow oscillations (SO, 1-4 Hz) constitute recurring temporal frames for the *hippo-cortical* dialogue, often associated with faster waves (10-16 Hz) lasting from 0.5 to 2 seconds, and referred to as *sleep spindles* (SS). Among many other functions, the calcium ion Ca^{2+} has long been considered as playing a leading part in the genesis of sleep spindles in thalamocortical (TC) neurons. But it was before testing the accuracy of SSs in genetically modified mice wherein the T-type Ca^{2+} channel has been disrupted (Lee et al., 2013). The TC tonic spike frequency revealed not to be increased during SSs, while those mice unexpectedly showed elevated anxiety and memory impairment (Gangarossa et al., 2014). Interestingly, this observation speaks for Ca^{2+} to be instrumental in learning-related physiological events associated with SSs, and therefore in the hippo-thalamocortical interplay

- Depolarization waves, spindles and ripples

Cortical spindles are likely local, may either coincide with SO up-states or occur independently in separate brain regions (Andrion et al., 2011). According to recent results, the coincidence of SO and spindles, named ‘SO-Spindle complex’, drives an endogenous memory reactivation likely propitious for previously encoded memories (Schreiner et al., 2019). Meanwhile, on the HP side, activity is concentrated in quick high-frequency *sharp wave ripples* (SPW-Rs) composed of a strong negative ~5-100 ms “sharp wave” superimposed on a transient signal named ‘ripple’, followed by about 200 ms positive wave (Buzsáki, 2015). A trend was found in rodents for hippocampal SPW-Rs to be phase-locked to both SS and SO (Skelin et al., 2021), which reflects a coupling between HP and cortical regions (Slapas & Wilson, 1998; Maingret et al., 2016), involving thalamic nuclei (Urbain et al., 2019), although the exact timing of these sleep signatures (i.e.: SO, SS, SPW-Rs) is controversial (Sirota et al., 2003; Ji & Wilson, 2007; Peyrache et al., 2009; Andrillon et al., 2011; Born and Wilhelm, 2012; Klinzing et al., 2019; Abadchi et al., 2020; Ngo et al., 2020). Of note, HP ripples, akin to fast *gamma* oscillations (40-80 Hz) in terms of frequency and amplitude (Sullivan et al., 2011), would not only accompany learning but also online retrieval (Hanna and Franck, 2018) aimed at decision-making, planning and imagination (Joo & Franck, 2018).

More precise data regarding ‘offline replay’ could recently be gathered in humans thanks to the simultaneous recording of electrical events in several cortical and HP areas. Both timing and spatial origin of these events contributed to identify new players in the *posterior* HP, named *spindle ripples* (SSRs) for “ripples phase-locked to local spindles” (Jiang et al., 2019). Known to preferentially encode detailed memories of lower-order sensorimotor information (Tang et al., 2020), the posterior HP emits multiple SSRs (one every ~80 ms) that are tightly coupled to the *posterior parietal* cortex, while the anterior HP encodes higher-order information with 10-time larger representational fields, and generates every 5 s a SWR mostly coupled to frontal activity. Following a theta burst, a SWR occurs ahead of a series of SSRs locked to SSs framed by SOs. To account for this specific signalling fosters the implementation of EEG-like histograms of global activity found in GP systems subparts.

- Two-stage model of sleep with segregated activity

In humans, HP ripples seem prone to frame cortical spindles, preceding them and distinctly decreasing afterwards (Clemens et al., 2007). Such apparent dependency between SPW-Rs and SSs sequences gives credit to the *two-stage model*, according to which novel information is first

encoded within HP during the waking state, and then replayed offline, enabling the consolidation of cortical engram associated with previous day-time experiences (Buzsáki, 1989, 1998) through the usual sleep-dependent plasticity (Puentes & Aton, 2017). Similar activity has however been reported to happen before experience (through “preplay”), suggesting that encoding networks would be pre-configured, therefore challenging the learning aim of replay (Dragoi and Tonegawa, 2011). High density recording methods have then contradicted this view by considering replay as a way to re-express “trajectory events” (Silva et al., 2015). Accordingly, whereas information is mainly driven from cortex to HP during wakefulness, sleep would favour streaming in the opposite direction, gated by global SO co-occurring in distinct brain regions. An overnight long-distance transfer of information between HP and cortex is nevertheless questioned by a reduced cross-communication evidenced between brain areas (Ferrara et al, 2012). Other data support different concepts than the original unidirectional link between brain regions. Refinements of the two-stage model notably include bidirectional flows of information involving loops (Rothschild et al, 2017), “*non-uniform timing of oscillations across the brain*” (Geva-Sagiv & Nir, 2019), and the observed noisy depiction of past actions wherein SWS replay is geared to the gradual consolidation of memory (Roumis & Frank, 2015). On top of that, a two-step timing of cortical hippocampal communication has been observed every 3-6 seconds (Helfrich et al, 2019), whereby cortical SO and spindles trigger SPW-Rs interleaved by silent intervals, refractory periods during which processing capacities would be maximized (Hanslmayr et al, 2016) thus “*safeguarding memory reprocessing from additional reinstatement*” (Antony et al., 2019).

- Slow wave sleep precedes paradoxical sleep

According to the *dual process* and *sequential* hypotheses, sleep stages would respectively deal with complementary types of engram, while traces formed in early stages would be stabilized and integrated within older memories during paradoxical sleep (Diekelmann & Born, 2010; Rasch and Born, 2013; Giuditta, 2014). Within every sleep cycle, SWS is first assumed to support declarative memory (Lee & Wilson, 2002) before PS would be busy with procedural and implicit ones (Ackermann and Rasch, 2014), although different tasks considered as implicit may not benefit from the same stages (Rauchs et al., 2005). On the modelling chapter, the decrease of two monoamines along SWS until their full absence during PS (Shouze et al., 2000; Monti and Jantos, 2008; Monti, 2011) was associated in GP systems to a gradual loss of anticipation ability suitable for proper encoding (Béroule, 2018). Elements of dreams are not restricted to the PS stage, although over shorter spans. Indeed, some ‘cortical replay’ occurs in all stages and cycles, ranging from “thought-like” in early-night SWS to ‘dreamlike’ in late-night PS (Cipolli et al., 2017). Despite large amounts of literature devoted to dreaming, the non-expectable nature of scenes that emerge from paradoxical sleep is still a matter of conjecture regarding both physiological medium at work and potential functions. Behind the PS scenes that are replayed, the mixing of characters and decors often breaks conditioning and time-space rules in a surprising, out-of-control manner. While the silence of controlling structures during PS is liable to weird associations, a possible close explanation arises from the aforementioned segregation between priming channels and sensorimotor ones, as well from other features of the model to be presented below.

Before probing into the GP model, a preliminary trial is worth conducting in order to estimate its potential for at least partly representing global traits of the sleep signalling introduced above. For that purpose, the global activity of selected GP modules was plotted for being compared with brain waveforms during the offline inner replay of previous online experience (Table 1). Additional information to follow may either confirm or dispel the mapping speculated there between GP channels *Hp* and *Cx*.

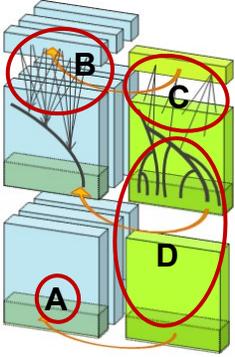
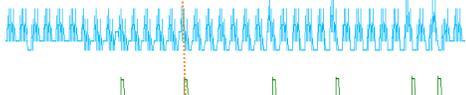
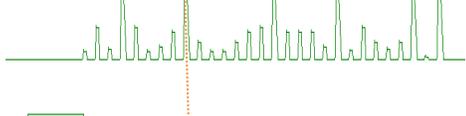
GP areas	GP global histograms of a replay	Brain signals	Brain areas
	<p>A </p> <p>B </p> <p>C </p> <p>D </p>	<p>Sharp wave ripples</p> <p>Spindle Ripples</p> <p>Sleep Spindles</p> <p>Slow oscillations</p>	<p>Anterior hippocampus</p> <p>Posterior hippocampus</p> <p>Thalamus/cortex</p> <p>Cortex</p>

Table 1. Parallel tentatively drawn between GP histograms of global activity and brain recordings in human (e.g.: Jiang et al, 2019). The left-most column shows the GP area concerned by each type of rhythm mediated at the bottom (**A**) of the *Hp* channel (in blue), propagating upward the periphery (**B**) where crosslinks allow *Cx* (in green) to get activated from its periphery (**C**) and downwards (**D**). In the 2nd column, the dotted orange line enhances the slight delay between synchronized signals akin to brain waveforms referred to in the 3rd and 4th columns. In figures to come, the underlying local signalling will be elicited by electrode-like recordings of individual network nodes.

3. A suitable model for representing both temporary and permanent memories

As a starting point, the cyclic alternation of online and offline processing stages was formerly proposed to govern the gradual growth of GP memory paths dedicated to the long-term encoding of events trajectories. In a previous study (Béroule, 2018), the decrease of parameters with “neuromodulating” effects across every sleep stage - consistent with the relationship between memory types and sleep stages (Rauchs et al., 2005) -, was shown to accompany the serial distribution of encoding among modules organized as depicted in the *ascending spiral model* (Haber, 2000), from emotional/conditioning to sensorimotor ones. Although still dealing with the sleep issue, the present computer-aided developments are centered on neural signalling that may underlie the hippo-cortical cooperation committed to memory formation. It appears that leaving the classical view of a single fixed network which implements synaptic plasticity turns out to be at the cost of more complexity on the part of the learning script and its underlying signalling. For the sake of simplification, the *Cx* part previously incorporating emotional and conditioning channels (Supplementary Fig. 4) is therefore reduced here to a single ‘sensorimotor’ channel.

3.1. Assignment of time-space memory locations through learning

Together with psychological knowledge on conditioning and priming effects, the time-space summation of local signals induced by afferent neural spikes at a neuron input had been a primary source of inspiration for GP networks: The more synchronized the inputs, the more effective the output. From this departure line, a distinction was made between two ways into Context-Dependent Units (CDU) acting as coincidence-detectors between inner/contextual flows and

stimuli defined by discrete time-space locations. A stimulus integrated by a given CDU may span from a single event such as a symbol (letter, musical note...), up to a cloud of spectral transient events (e.g.: speech map). Owing to the leading role of coincidence detection in GP, free CDUs are used for intersecting stimuli and contextual flows as both expand with experience. Consequently, an instant stimulus will concurrently feed as many CDUs as different contexts encountered so far, while every CDU will (pre)activate as many downstream neighbour CDUs as number of stimuli to possibly occur next. Whereas successful meetings between incoming stimuli and propagating inner flows characterize the system regular behaviour, the fact that a stimulus **S** does not receive an ‘acknowledgement of receipt’ (e.g.: backward facilitation that triggers a reset) from a CDU means that **S** had not been expected beforehand. For **S** to be later anticipated when the same context happens again, the relevant GP module is upgraded by hanging up a new CDU to its currently active memory path. This has to be done at the right location, hence the requirement for a ‘restricted propagation mode’ that prevents ambiguous widespread activity from causing erroneous connections.

3.2 Coincidence detection between activation, inhibition and facilitation

Unlike *Perceptron* and its descendants wherein feedforward activity spreads across layers from input to output vectors, GP systems cannot run without spontaneous inner flows that convey contextual information. Located inside a 3-D structure composed of channels, storeys and slices, each GP module can be viewed as a memory folder for a specific cluster of serial patterns (see: Supplementary file). A module internal activity (P0) can selectively be guided downstream towards its output formed of Pattern Detectors/Generators (PDGs), while *sensors/effectors* PDGs stand at the interface between a GP system and its environment. Guided propagation involves facilitating drops in response-threshold (P1) and direct stimulation (P2). Similarly, each module output is also a higher-order stimulus for the deeper storey (P2), and so on, yielding compound/embedded/ hierarchical representations within a given channel. Accordingly, the deeper the storey, the longer the stories it can learn and tell. GP is locally controlled by a couple of dynamic parameters attached to every unit (i.e.: contextual weight and global excitability). P0 can thus be induced to flow along paths that are temporarily facilitated (P1), and at the pace of stimuli produced by more peripheral modules (P2). P0 is also narrowed in space and time through *lateral inhibition* (P3) which primarily resets short-term anticipations that are conveyed in parallel by P0 streams in every module. Interestingly, the possible coincidence of P1, P2, P3 is instantly detected, regardless of the size of involved memory subsets.

Owing to the GP architecture homogeneity, a given path can support both primed/gated perception and selective generation of actions paced by proprioceptive stimuli feedbacks. Of importance in the present study, any recorded trajectory can indeed be replayed thanks to P1 *backward facilitation* (threshold drop propagating upstream memory paths) whereby the inner flow P0 is selectively pulled towards a PDG target. Offline, P0 cannot be guided by environmental stimuli occurring at variable rates, but instead by immediate feedbacks from pre-activated peripheral sensors/effectors, which results in a fast production rate only constrained by the algorithm processing steps. Table 2 lists the different local responses that may occur in GP systems, and Table 3 displays the basic activity histograms computed while a 3-event trajectory is recorded and then generated (either by the same STM channel or by the LTM channel).

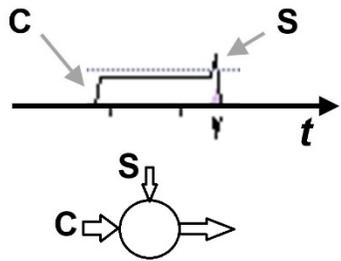
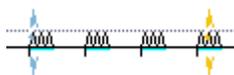
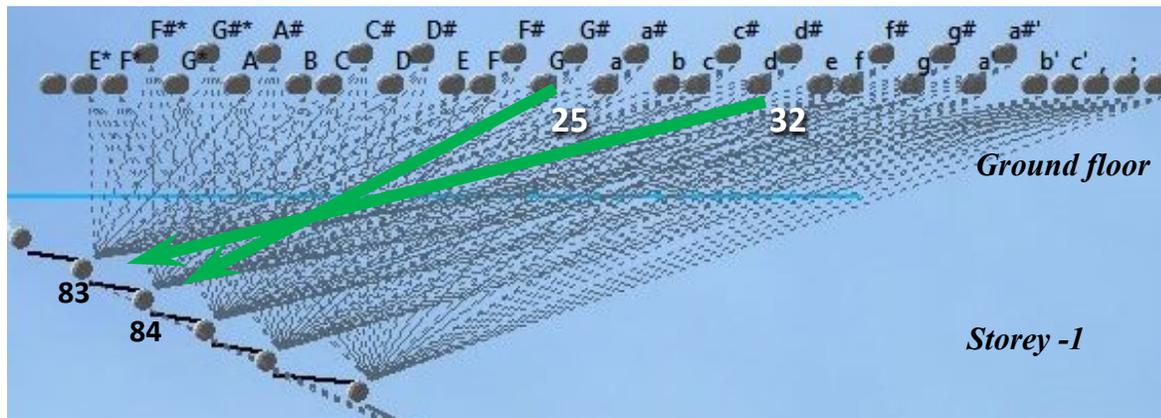
Processing	Coincidence detection
Tonic pattern processing: Long-Term Memory (LTM)	
<p>At the input of a Context-Dependent elementary processing unit (CDU at the bottom), a tonic contextual signal (C) occurs here ahead of a stimulus (S), as shown by the activity histogram. When C+S cross the CDU response-threshold (dotted line), the resulting output (downward arrowhead) plays in its turn the part of contextual signal for next CDU downstream.</p> <p><i>Role:</i> LTM pattern-matching through coincidence detection (Figs. 1, 3, 4, 5, 6).</p>	
<p>Tonic facilitation lessens a threshold at time t_1, without any effect until activation occurs at t_2. Beginnings of stimuli or contextual signals are respectively emphasized by a purple or a pink underlining.</p> <p><i>Role:</i> LTM pattern-production (Figs. 5, 6)</p>	
<p>Tonic pre-activation (horizontal line above the time axis) and facilitation (drop of threshold indicated here by two dots). The post-response red line beneath the time axis stands for a refractory period.</p> <p><i>Role:</i> Output LTM pattern-production (Figs. 5, 6)</p>	
Phasic Production: Short-Term Memory (STM) replay	
<p>Tonic facilitation of phasic bursts produced by a central memory path.</p> <p><i>Role:</i> Launching of STM replay (Figs. 3, 4, 5)</p>	
<p>Tonic activation undergoing phasic threshold drops (instant facilitation at the coloured dots) aimed at spreading upstream the host channel (upward arrows).</p> <p><i>Role:</i> Central STM replay (Figs. 3, 4)</p>	
<p>Phasic threshold drops meet waves of phasic bursts and generates responses.</p> <p><i>Role:</i> Peripheral STM replay (Figs. 3, 4)</p>	

Table 2. Outline of local signalling in GP systems, as excerpted from screenshots of computer simulations. Typical combinations of signals are introduced here to ease further reading of full histograms displayed in next figures. Coincidence detection is performed by every network node (i.e.: elementary processing unit) between distinct inputs whose shape is either tonic or phasic, and which impact either the response threshold (facilitation) or the activity level. Every time a unit threshold is found below its activity level, activation spreads downstream towards central modules, and a threshold drop propagates upstream towards peripheral modules. The arrowheads colors indicate the phases of these responses within the phasic period separating two marks below the time axis.

In the following, computer experiments will encompass fifty short temporal patterns (i.e.: series of notes) to be encoded within a GP storey (-1), and forming ten compound patterns (i.e.: entire melodies) aimed at feeding a deeper storey (-2). As a memory path is built, its label results from the automatic concatenation of its components' labels, initially only assigned 'by hand' to the ground floor units akin to musical notes. In this way, the learning algorithm can be assessed by final labels having been dynamically attached to the 'storey -2' memory paths, that should eventually correspond to the melodies formerly input into the GP network.



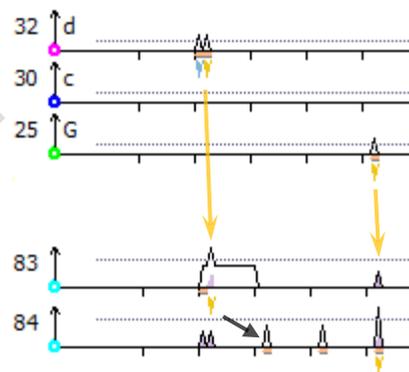
phasic binding and topological coding

Histograms of processing units

A/ Recording of successive stimuli

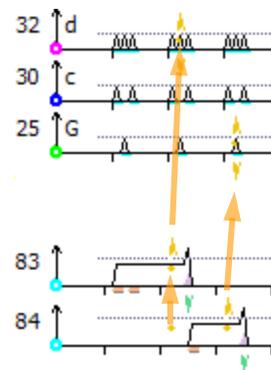
In the window above, ground-floor input/output units of the 'Recorder-Player' phasic channel *H_p* are connected to a generic path of Storey-1, including nodes 83 and 84.

The top 3 diagrams respectively display the activity of input/output nodes, including the one labelled 'd' (n°32) previously bound to phase 1 (in blue) and tentatively given a second phase (in yellow). Each downward yellow arrow represents the transmission of an instant stimulus. The left-to-right black arrow between histograms 83 and 84 stands for a contextual signal that streams onward the generic path.



B/ Inner replay of the same sequence of stimuli

The top diagrams show the cyclic activity of the same input/output once several patterns have been recorded. Upward orange arrows represent threshold drops that spread upstream the same phasic channel. The number of pulses periodically released by a CDU corresponds to as many patterns it currently supports (e.g.: 2 patterns for unit 30). Here, the 2nd phase (in yellow) is triggered by the same units as in A/ (83 and 84) through drops in thresholds.



C/ External reactivation from a Cx distant channel

Once a ‘private path’ has grown in an LTM remote channel, it is played so as to reactivate its *Hp* phasic counterpart(s). Thresholds at the top undergo tonic facilitation from the tonic channel ground floor (see Fig. 7), which triggers activation downstream *Hp*.

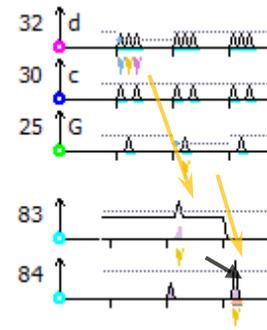


Table 3. The same generic GP path whose histograms are plotted here can record (A/) and replay (B/) as many patterns of stimuli as available phases. Replay is aimed at growing a specific Cx path. Then, replaying the latter (C/) reactivates the same generic path and allows cross connections between the just-completed path and its *Hp* generic generator.

3.3 Topological encoding compromised by the anticipation skill

Besides consciously remembering of the past, automatically and instantly matching the current context with previous experience stands at the core of anticipation, a time-dependent skill amazingly supported by the spatial distribution of brain cells. From myopic foreseeing to forecasting the distant future, from unconscious to attentional processing, experience-based expectations condition proper behaviour, not mentioning survival. Along GP paths mapped onto the time dimension, sparsely activated units represent a snapshot of the present situation, while possible future events are primed ahead of their time by means of ‘depolarizing waves’ (P1) stemmed from conditioning/emotional folders. A Pavlovian effect results from this partnership, whereby activation in conditioning modules spreads ahead of schedule, enlarging the subset of their active units through ‘extended propagation’. Such outcome is not compatible with the growth of new GP paths, for the latter relies upon the precise tracing of coincident activities. Deprived of other channels influence, decision-making cannot then be primed (segregation). This strong learning constraint brings in the option of periodically calling offline states wherein priming/anticipation is useless: the online interaction between channels that contain permanent traces is dismissed. LTM formation can be postponed on condition that significant data are recorded by a specialized subsystem with suitable modulation, namely a hippocampus-like channel running in the “restricted propagation” mode, while cortex-like GP folders compute the same situation in the “extended propagation” mode that underlies anticipation. As an illustration of the true contradiction between anticipation making and integration of add-on cells, the GP model of autism implicates faulty modulation during offline periods (B eroule, 2016, 2018).

3.4 Instant binding of events through synchronized activity

Before being considered here as a STM medium, pulse signals with distinct phases had first been implemented in a GP network in the context of multimodal processing (Martin, 1994). In a later application to syntactic parsing, characteristic phases were dynamically associated to instances of the phrases that compose a sentence: The sentence parser/generator developed in 1998 at the University of Sydney learns recursive syntactic structures from examples of increasing complexity: elementary phrases before embedded expressions, as reported in (B eroule, 2004). Then whenever a known phrase (e.g. noun, relative) is computed, the phase at which the relevant path gets activated is shifted, which enables the same path to concurrently host several recursive calls without interference until sentence completion. Different instances of the same syntactic

structures can thus be treated through phase coding without memory hardware upgrade, until an unexpected class occurs that triggers the growth of a new path with embedded cells. When implemented in this manner, phasic information was viewed as a ‘secondary messenger’, behind the allocation of specific memory paths to as many patterns. Henceforth inverting coding priorities leads to the architectural gist of the present *Hp* model, namely *a generic path, fully connected to sensors/effectors, wherein patterns of phasic activity can instantly be bound and replayed* (Fig. 1). To the extent that biological mechanisms exist that underlie this micro-temporal coding, the latter compensates for the non-specific origin of stimuli that all converge towards a generic path. Within the host GP channel akin to HP (i.e.: *Hp*), generic paths instantly encode sequences of PDG activity identified by as many characteristic phases within a peripheral storey, and a combination of these very phases in a deeper storey (Fig. 2). Every resulting labile trace is retained as long as the subset of its supporting components (i.e.: GP units and links) can remain tuned to its characteristic phase. Beyond the duration of this tuning, the range of available phases determines the STM span, an issue resolved in two ways: One is to take advantage of other *Hp* slices containing generic paths plus their bank of input/output PDGs. The second solution is to recycle phases once they have contributed to *Cx* extension.

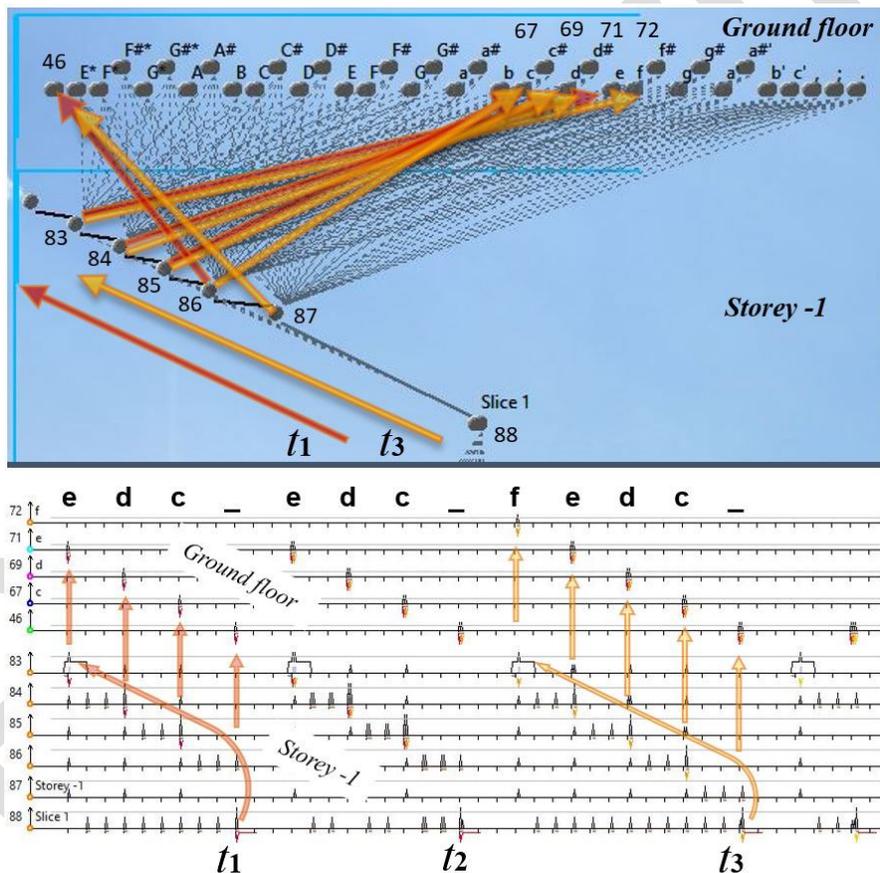


Figure 1. Assignment of characteristic phasic signals to events trajectories, namely here: elementary series of notes (melodies). The screenshot to the top shows the network of Table 3 while its elements are being tuned to a couple of distinct phases for two melodies (“e d c _” and “f e d c _”). Involved connections between the bank of detectors/generators (PDGs) at the ‘ground floor’ and the underneath ‘Storey -1’ generic path (nodes 83 to 88) are plotted by links with two different colours. Activity histograms show the propagation of signals issued from the path spontaneous activity and incoming stimuli (shown at the top). Subsequent backward facilitation (thick yellow arrows) allocates a phase to the very nodes and links that

just contributed to the path activity. In this way, the subnetwork fed with “e d c _” receives the 1st available phase (in red) at time t_1 . At time t_2 , the beginning of the “e d c _” pattern brings a new phase (in orange) added to its previously assigned phase all the way down the final node (n° 88) whose *refractory period* (red underlining) inhibits the provisional phase. “f e d c _” is then integrated at the next ‘candidate phase’. At time t_3 , the ‘orange phase’ can this time reach the end of the path without being inhibited and becomes the signature of “f e d c _”. Because phase allocation is performed while CDU remain partly activated, their associated stimuli are regenerated at the speed of the backward signal, in a fast reverse order.

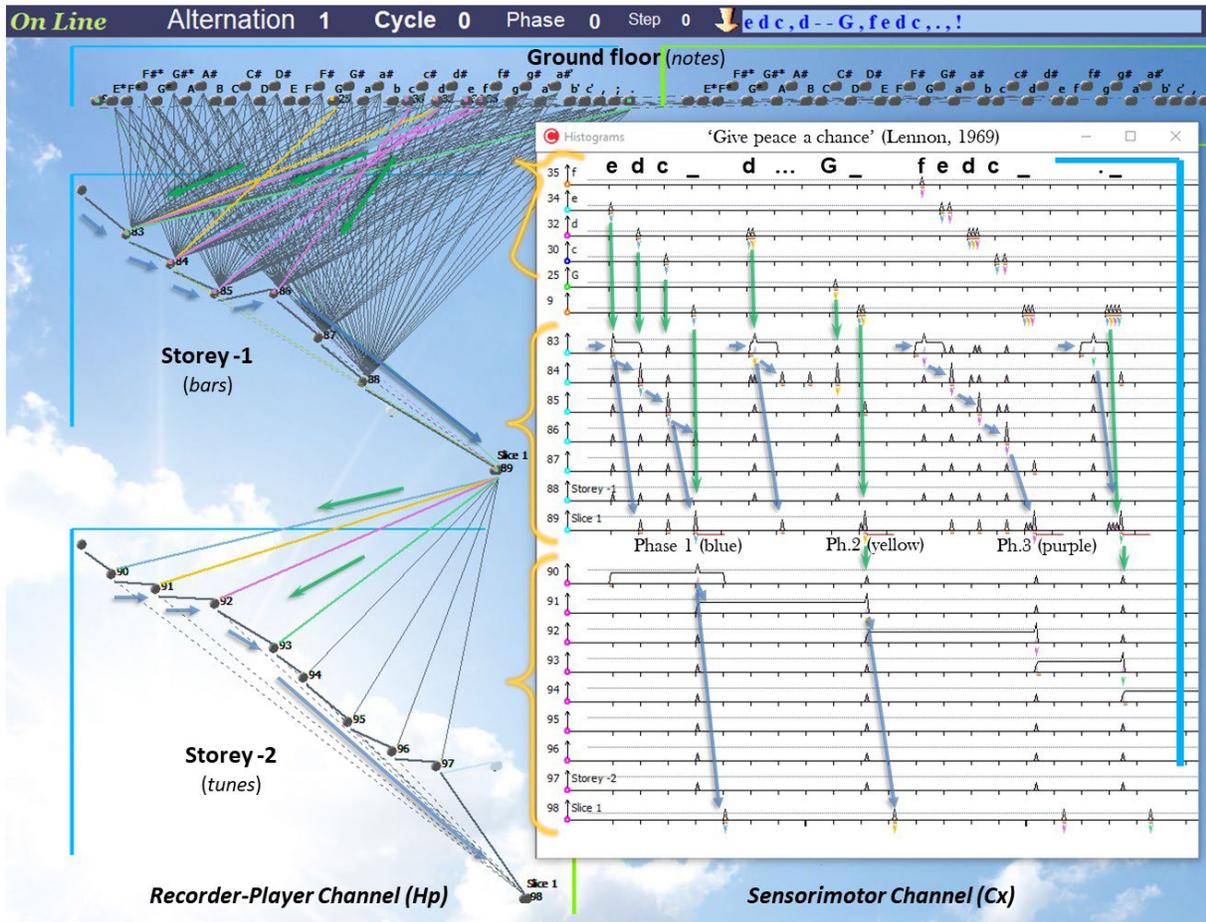


Figure 2. Instant record through phasic binding of a full melody (in Storey -2) made of short series of notes encoded in Storey -1 from banks of PDGs coding for notes (Ground floor). Arrows superimposed here on a screenshot of the relevant histograms follow conventions given in Tables 2 and 3. To the left-hand side, colors of links and units indicate the phases to which they are being tuned. Pulse signals generated at the bottom of the ‘Storey -2’ will offline be grouped in time before undergoing threshold drops for repetitively replaying the same melody (Fig. 3) and cause LTM paths to sprout in Cx (Fig. 4).

3.5 Memory channels interplay across online/offline cycles

Owing to their common GP substrate, Cx and Hp should be amenable to exchange information, albeit through a plan to be delineated. In the brain, hippocortical interactions are likely mediated by a hub-like structure, be it thalamic (Hwang, 2017; Yang et al., 2015) or cortical such as the *subiculum retro-splenial pathway* (Nitzan et al., 2020). Before deeper cross-connections are gradually built between channels, the lowest level of input/output (i.e.: sensors, effectors PDGs) first ensures essential communication: Each peripheral PDG is initially linked in this respect to its

homonyms present at the entrance of other channels. A global scenario of memory formation can be derived from this initial architecture, and simulated on computer (see video screenshots taken over computer sessions: Bérroule, 2023).

3.5.1 Online immediate *Hp* records

On-line, *Cx* and *Hp* channels are concurrently stimulated by the same input. With resort to phase-coding, a *Hp* channel is recording significant events on the fly (STM) while *Cx* is busy matching the same events against its inner references on one hand, as well as foreseeing possible events to come on the other hand. Thanks to crosslinks created between *Cx* and *Hp* paths at the time a *Cx* path is completed, the graduated output level (i.e.: tonic signal) of the latter tells its *Hp* partner how much the present input pattern matches its current *Cx* reference, thanks to activation scores resulting from the incremental weighting of *Cx* paths (Westerlund et al, 1996). Given that a new input may only differ from a known pattern by a final stimulus, this is only at the end of an ongoing trajectory that the relevant phase assignment can be acknowledged by the *Cx* channel, namely if none of its existing paths has concurrently been activated.

**Hippocortical interaction n°1: Online *Cx* => *Hp*
Cx avoids the phasic encoding of known events/trajectories**

A turnover process controls the reassignment of a new phase allotted by-default to a pattern that turns out to be already known (Fig. 1). Processed by the *Hp* slice which is currently active, an incoming series of stimuli is therefore temporarily assigned an extra phase, waiting for the impending *Cx* verdict: This assignation is confirmed if *Cx-Hp* cross-connections remain silent, because no existing *Cx* path was activated enough by the pattern at issue; the ongoing phase is otherwise dismissed until being recycled through its next tentative attribution to the upcoming input. When an online state ends, only phases of non-acquired episodes remain active for being replayed offline. In case of either inhibition by an earlier phase (Fig. 1) or nearly-full activation of a *Cx* path, the *Hp* phase currently involved in STM encoding is freed and thus made ready for binding elements of the forthcoming input.

3.5.2 Offline recurring replays

Off-line, *Cx* units' parameters gradually fit in the "restricted propagation" mode that ensures proper growth of GP paths. *Hp* deep-storey PDGs express subthreshold spikes at their characteristic phases so as to be ready to generate relevant patterns through subsequent selective depolarization (P1). Of note, subthreshold spindle oscillations have been found in the somatosensory thalamus of rodents, which partially overlap cortical spindles (Urbain et al., 2019), consistently with GP histograms (Table 3 B/): the *Hp* ground floor that must receive subthreshold spiking across replay, and the *Cx* ground-floor which expresses local signals mimicking a spindle-like oscillation once they are summed (Table 1). Thanks to the cross-connections between ground-floor PDGs, offline *Hp* productions sound for *Cx* as if coming from the outside world, albeit at the highest possible rate only determined by inner mechanisms (Fig. 3), in line with the apparent time-compression observed during HP offline replay (Euston et al, 2007). Across the offline period, waves of phasic facilitation can repeatedly flow upstream an *Hp* deep generic path (in storey -2) in

order to broadcast the phasic patterns towards *Cx* channels, among which some are ready to extend their memory paths.

Hippocortical interaction n°2: Offline *Hp* => *Cx*
Hp* is replaying trajectories to be learnt by *Cx

Provided a reservoir of unemployed cells, *Cx* benefits from *Hp* rehearsing periods for sprouting new paths (Fig. 4). Since their sprouting rate lags far behind the swift *Hp* productions, a given *Cx* path may only differentiate step-by-step at each *Hp* replay of the trajectory it is encoding (See video: B roule, 2023). After the reset of *Cx*, its inner spontaneous activity is launched. Whenever the relevant same trajectory is replayed by *Hp*, its *Cx* path activation is reinstated so as to possibly resume sprouting from where it had proceeded so far. Once fully built, a new *Cx* path is played in turn, which makes *Hp* respond slightly later, inducing a feedback connection between the new *Cx* path end and its *Hp* generic counterparts inside all slices (Figs 4 and 5), cross-circuit that allow then the aforementioned ‘‘Hippocortical interaction n 1’’ during online phases.

Even though the final outcome compares to a transfer of information, online records are rather rehearsed offline, and their long-range storage in distant and parallel folders (*Cx*), once completed, eventually relieves *Hp* from its ‘‘buffering’’ role. Of note, for HP traces to be fully translated into cortical ones, the observation of engram cells showed that a few weeks are required before the latter are functionally, structurally and physiologically matured under HP action which would stop afterwards (Li et al., 2017).

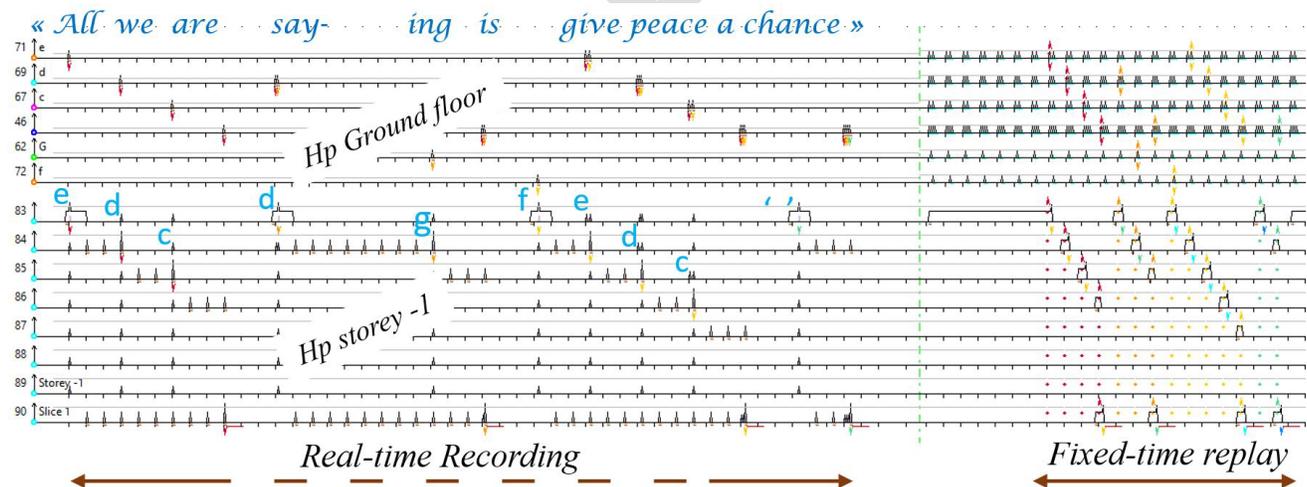


Figure 3. Offline fast replay (to the right-hand side) of a melody previously encoded online at the pace of incoming notes, as witnessed by histograms of the relevant *Hp* paths. Resulting from threshold drops triggered by ‘Storey -2’ (not shown here) and crossing ‘Storey -1’ (CDUs 83-90), phasic bursts occur in the 6 top-most diagrams and activate the *Cx* input/output (see Fig. 4). Whatever the rate at which this sequence was recorded (here twice the original tempo), the duration of its replay is determined by the quick successive feedbacks from stimuli.

In order to possibly learn embedded trajectories, a compound one (e.g.: a full melody) cannot be learnt before all its elementary components (e.g.: short series of notes). The completion of an elementary pattern activates its new *Cx* pathway, which is conveyed to its *Hp* partner. Once all

patterns memorized by the relevant *Hp* path have been transformed into *Cx* memory paths, the latter are allowed to be learnt by the deeper *Cx* storey that contains compound patterns.

Hippocortical interaction n°3: Offline $Cx \Rightarrow Hp$
Hp* generic path is notified that all its phasic patterns have been learnt by *Cx

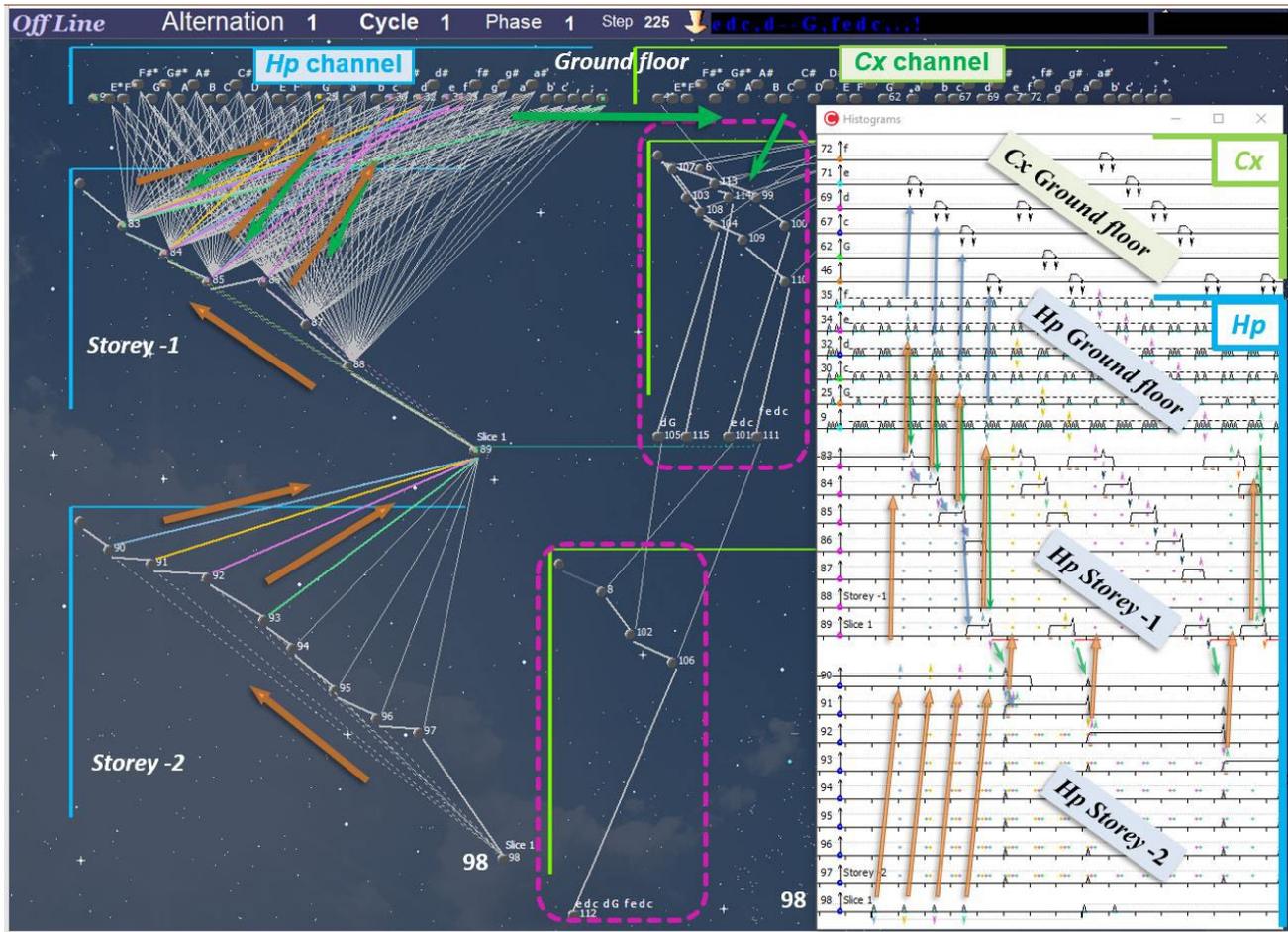


Figure 4. *Cx* long-term memory issued from the repetitive replay of phasic patterns that were previously recorded (Fig. 2) by *Hp*. To the left-hand side, while ground-floor subthreshold bursts are continuously generated at phases assigned online, facilitation (orange arrows) of the *Hp* channel is initiated at the bottom of Storey -2 (node 98). This upward selective facilitation makes a few pre-activated ground-floor units fully respond (see: '*Hp* ground floor'), thus bringing about relevant tonic signals at the *Cx* channel input (top histograms at the '*Cx* Ground floor'). The GP learning algorithm detects unexpected inner stimuli for creating new paths that get eventually connected to their *Hp* generic partner (blue dotted lines). Arrows superimposed on histograms show the propagation of threshold drops from the 4 phasic pulses at the bottom up the *Hp* ground-floor, hence the *Cx* ground floor signals. The consequent pattern of activity at the *Cx* input has here given rise to specific/private paths (framed by purple dotted frames) in the two storeys.

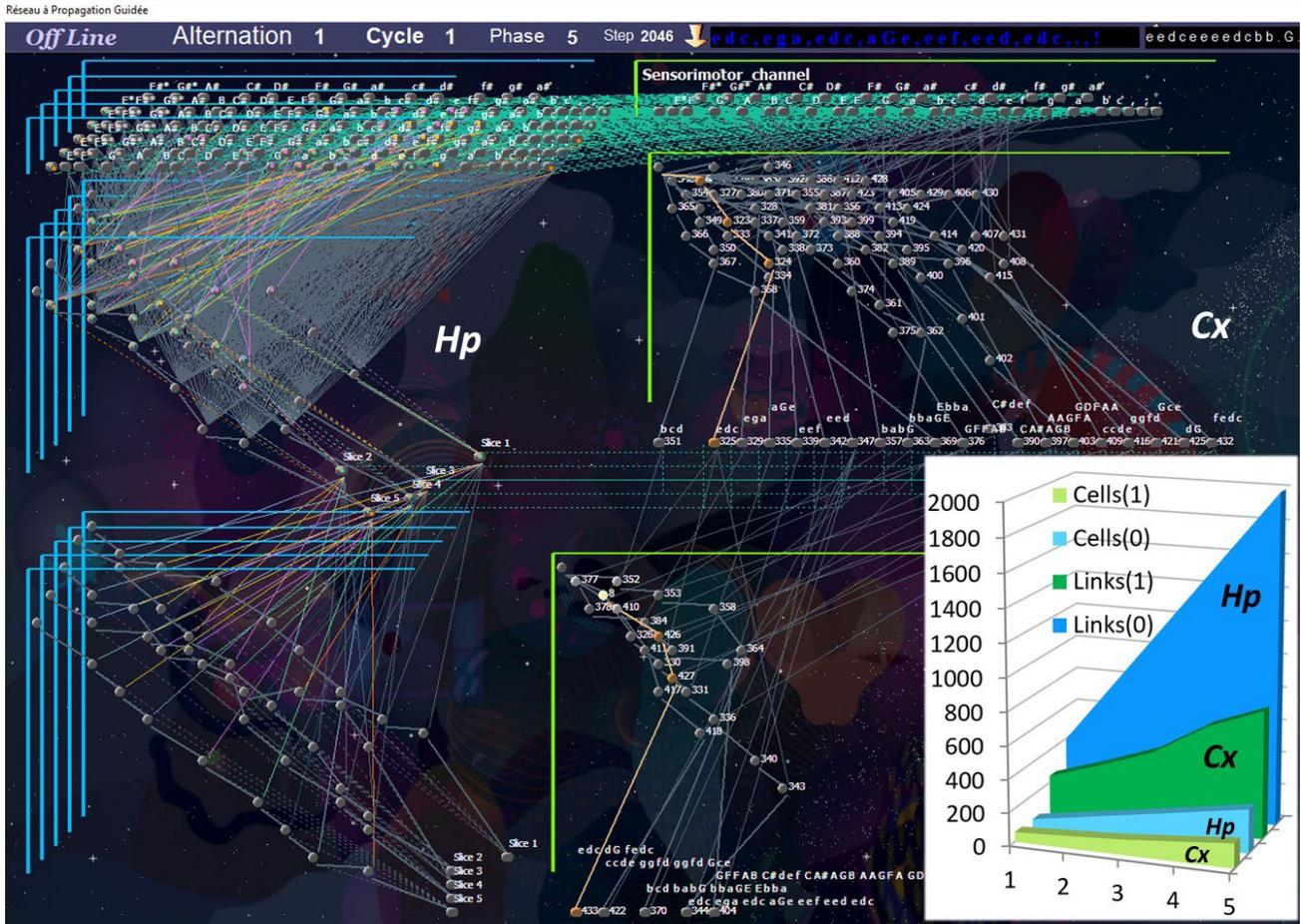


Figure 5. Comparison between STM and LTM media that have been subjected to the same input, either directly online or trough offline replay. To the left-hand side, 5 slices of generic paths are respectively keeping track of 5 patterns through phase coding. To the right-hand side, two *Cx* paths (in orange) are currently replaying one of these patterns, within the last phase of an offline cycle (representing paradoxical sleep). The graphical plot shows that once STM has been converted into LTM, the *Hp* generic paths have used about twice more resource in terms of cells and links than the *Cx* specific paths. However, the same generic paths being reusable, they will support the swift storage of future events.

3.6 Projection of the model into neurobiological data

After having proceeded to the offline state while its owner is having a rest, the brain is far from inactive. Freed from the control of behaviour encompassing anticipation, it can properly translate memories of previous experiences recorded by the hippocampus into cortical permanent imprints. One puts forward that the latter may result from the step-by-step growth of GP memory paths. This hypothesis raises the issues of whether - and possibly how - the cortical hardware could support such dynamic learning. Before addressing this central point, the GP model features can already be mapped onto the aforementioned neurobiological fact and hypotheses (Fig. 6). For now, persistent engram is likely hosted by cortical regions, in which dormant cells form potential add-on units (link 1 in Fig. 6).

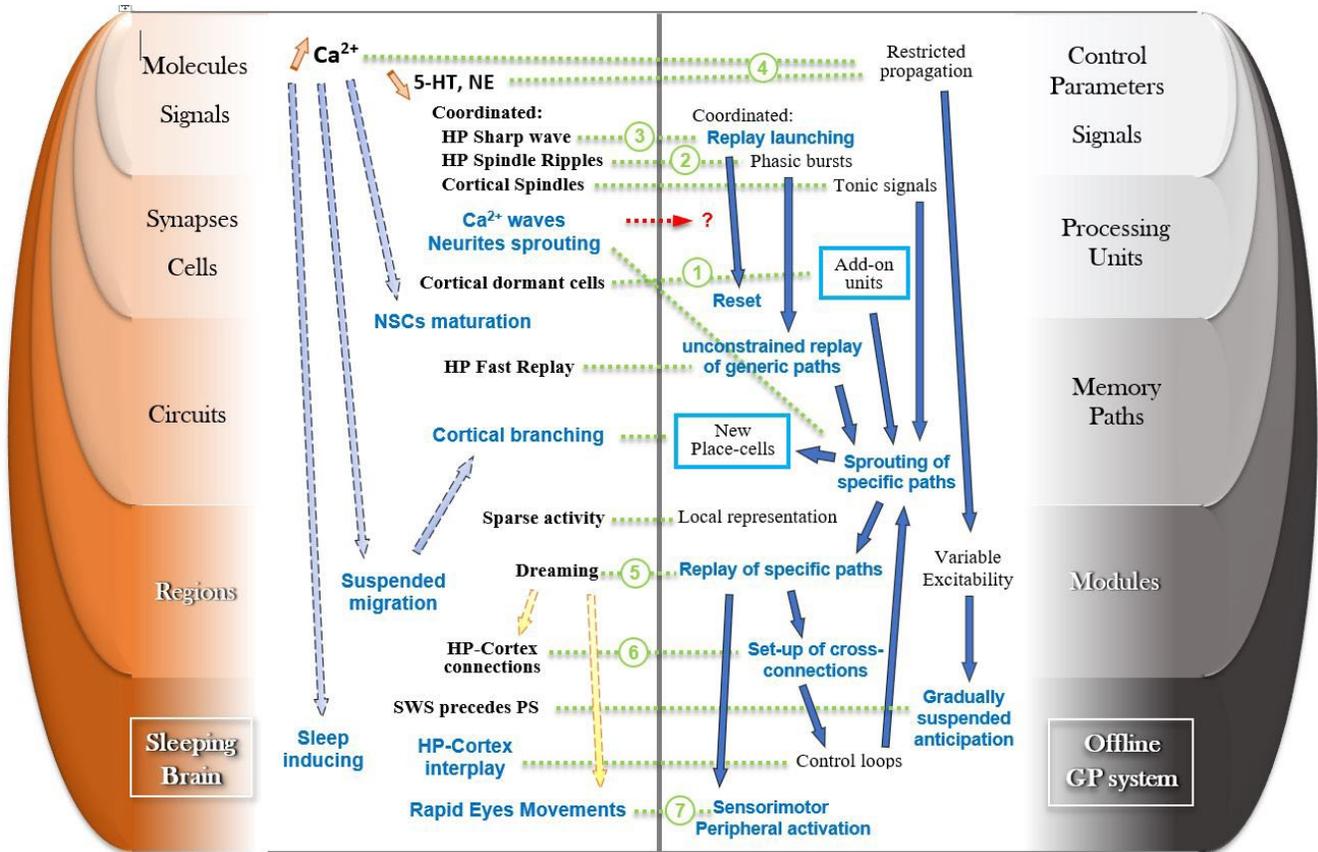


Figure 6. Recapitulation of facts and processes integrated across the functional levels of two learning systems (i.e.: biological next to the GP artificial model) while running offline. Relevant representations respectively occupy the left-half and right-half of a five-level hierarchical framework, ranging from low-level molecules/parameters at the top to the full systems at the bottom. The dotted green lines tentatively associate features from one side of the figure to the other. The dotted red arrow indicates a missing link to be addressed in the final section 4, namely the axonal sprouting issue. Blue arrows indicate causal relationships between reported phenomena, which are only definite on the computational side (plain lines against dotted lines on the biological side). By projecting the known cause-effect pattern from the right to the left-hand side, connections can be predicted between biological correspondents (e.g.: yellow dotted arrows mirroring blue arrows).

3.6.1 Signalling between *Hp*/HP and *Cx*/cortical area

Although different in nature, offline GP plots (Fig. 1) exhibit coordinated/locked activities that recall the timing of HP ripples and cortical signals (Jiang et al., 2017, 2019). Assuming that the duration of spindles matches the fast environment-free replay of sequences, the depolarization of ‘anterior HP’ ripples compares to the series of GP threshold decreases required for trajectories to be produced. Ripples could thus spark bursts at characteristic phases for generating as many patterns (link 2 in Fig. 6). With respect to the close timing of the two channels under consideration, the earlier rising of *Cx* - relatively lengthy and powerful - spontaneous activity is monitored here in first place for simulating the “audience” attention to *Hp* channel performance. Contrary to a shared assumption, GP running simulations hence show that the first active window to open among involved regions does not necessarily indicate the origin of an “information transfer”, nor its prominent/leading role (link 3 in Fig. 6).

3.6.2 Replay in either original or reverse order

Unlike the direct transfer of information usually assumed from HP to other areas (Kitamura et al., 2017), *Hp* sparse activity is strictly speaking “re-generated” and widely broadcasted towards all *Cx* channels, although each of these only captures information it is sensitive/“tuned to”. Analogous to depolarization is a wave of phasic ‘negative bursts’ undergone by response thresholds, which, when applied to a generic path connected to pre-activated effectors, generates events previously bound by the same phase. As this modulation signal (i.e.: *backward facilitation*) flows upward the *Hp* generic path, depending on the resting activity level of CDU components, events will be produced either in their original or reverse order, which evokes the dual replays observed across brain states: the original order during sleep, and both ways in the awake state (Findlay, 2020). Consistently, the GP online replay that follows the storage of a new pattern merely serves the allocation of a characteristic phase to all involved CDU, irrespective of their scanning order. This is different from offline productions which must drive parallel channels in the right order, so as to connect their last activated (PDG) units, incidentally stimulating *Hp* and eliciting dream-like memories (link 5 in Fig. 6). The aforementioned replay of a just-finished *Cx* path activates its generic *Hp* partner slightly later, yielding a cross-connection between them (blue dotted links in Figs. 4 and 6; link 6 in Fig. 6).

3.6.3 Necessary priming of lowest-level sensors/effectors

According to the above, any just completed *Cx* path has to be reactivated, including longest paths at the end of every offline cycle akin to PS. This function is worth contemplating with regard to the challenging situation of a perception-oriented device that finds itself offline short of stimuli whereas their proprioceptive feedback is however required to work as pacemaker. This is why the sub-threshold activation of all the *Cx* most peripheral detectors/effectors must be achieved beforehand along PS for enabling activity patterns to reach the *Hp* channel where a generic path must concurrently be reactivated (link 7 in Fig. 6). Consequently, some of these primed PDGs become fully activated and consequently produce elementary actions (e.g. close to the scanning of scenes in the case of visual PDGs). Projected into the biological context, this process may logically not only trigger the wake-like activity of vision effectors, but also the mobilization of audition active components such as *Outer Hair Cells* (Brownell, 1990; Cooper and Guinan, 2006). The acoustic dimension of dreams would then rely on this phenomenon predicted by the model.

3.6.4 Dream features

In preliminary computer trials, dream-like unexpected patterns have been observed across *Cx* replay with tonic signals, partly due to their ambiguous translation into the phasic language spoken by *Hp*. Indeed, a *Cx* tonic signal covers all the *Hp* phases. At the ground floor, translating the tonic activity from *Cx* into phasic pulses aimed at *Hp* involves a square signal that spans the full phasic period (Fig. 7). Furthermore, every *Hp* slice being stimulated by a *Cx* replay, all occurrences of a given pattern will get activated regardless of the chronology of the slices. Accordingly, this would allow elements of distinct “life periods” (e.g.: *semantic frames* in “core slices”) to pop up across any such cortical replay. Ambiguity inherent in the generation of phasic signals by tonic ones is liable to *Hp* over-activation, for every stimulus occurrence can get aroused in different slices, irrespective of its original – and meaningless - phase assignment (Sup. Fig. 6). Besides, the offline depressed modulation can weaken the contextual input to CDUs, causing untimely intrusions of stimuli into the ongoing story. However, and against expectations, the actual outcome of multi-module and multi-coding offline replay turns out to be reliable, and even faithful to the patterns

previously recorded online. Computer simulations confirm that the over-activation of several ‘Storey -1’ slices is harmless as long as their associated ‘Storey -2’ selects the correct combination of elementary patterns, which results from the “robustness to noise” feature of GP systems. A related potential cause of dream-like behaviour is worth mentioning: Unlike *Hp* and its fixed couple of storeys, *Cx* channels allow deeper storeys being dug. Consequently, the deepest *Cx* storey facilitated at the end of an offline cycle will activate *Hp* short-span memories that are not linked through long stories able to “filter noise”. Dreams may therefore serve the generation of scripts derived from existing memories, which would prepare to better experience similar scripts with a feeling of “d  ja-vu”. Memorized combinations of never-encountered events could then be considered as “pre-played” when followed by their actual online occurrence, consistently with the aforementioned “preconfigured local network” (Dragoi & Tonegawa, 2011).

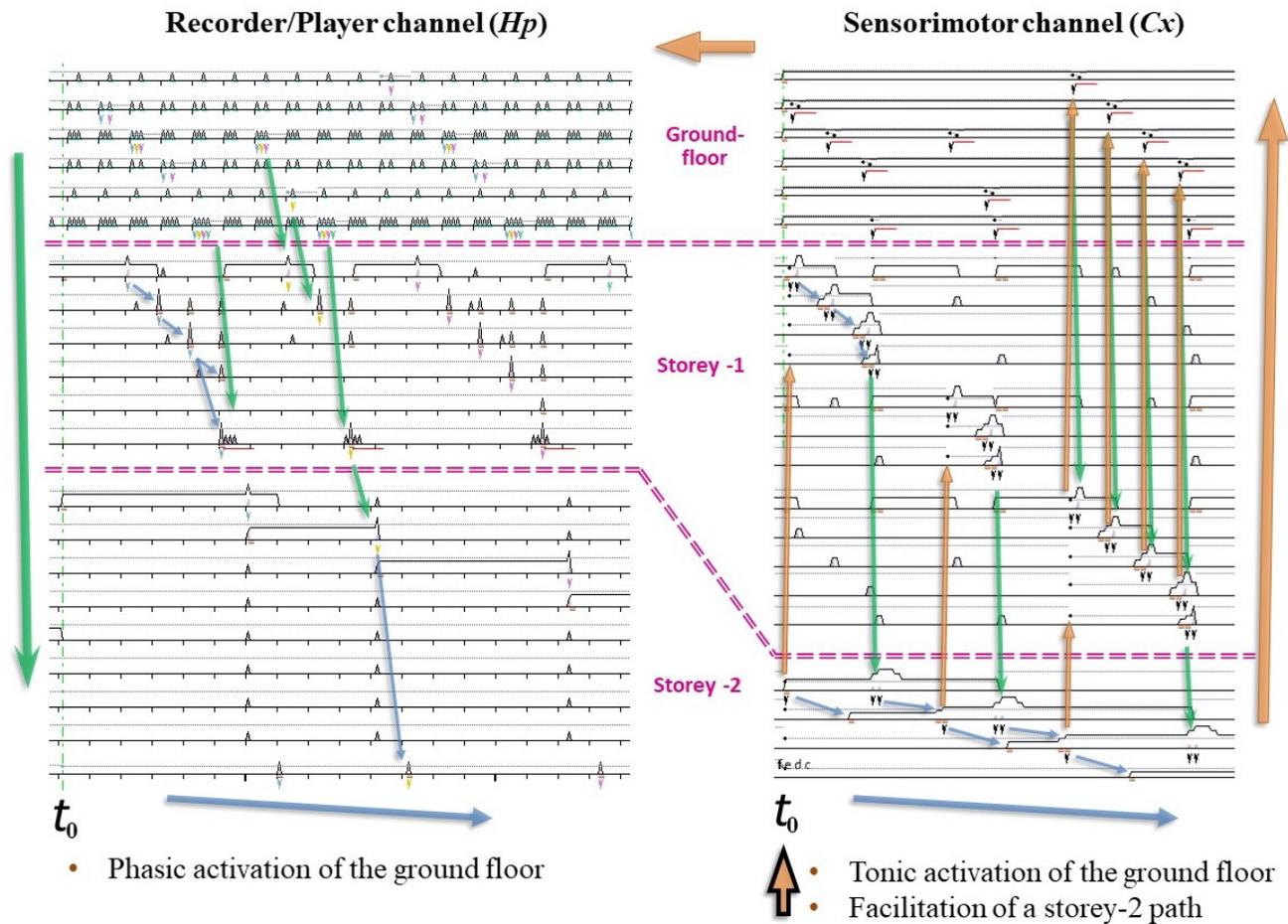


Figure 7. Replay of a deep *Cx* path (storey -2) during the offline cycle akin to paradoxical sleep. At time t_0 , both *Cx* and *Hp* channels are first fed with spontaneous activation ahead of *Cx* tonic facilitation (orange arrow at the bottom-right) that triggers the displayed streaming upward *Cx*, towards the peripheral ground-floor. At the same level (top of the figure), threshold ‘square drops’ of *Hp* PDGs are induced by their respective *Cx* correspondents. The resulting time-space pattern of stimuli spreads down the *Hp* storeys in a way comparable to the actual occurrence of the same stimuli stemming from the outside world.

4. From modelled functions to neurobiological structures

As an abstract representation of memory formation, the GP model implements add-on units prone to integrate the memory medium on learning demand. Furthermore, LTM updating would happen during offline time frames, which is challenging for the physiological likelihood of Cx when knowing that neurites growth rates, depending on the nerve type, have only been found in the range of 20 to 75 $\mu\text{m}/\text{h}$ with pick velocity of 100 $\mu\text{m}/\text{h}$ (Aquino et al., 2012). Additional data deserves nevertheless being called upon to investigate whether structural/anatomical counterparts of the GP functional/computational model exist that would satisfy these very constraints.

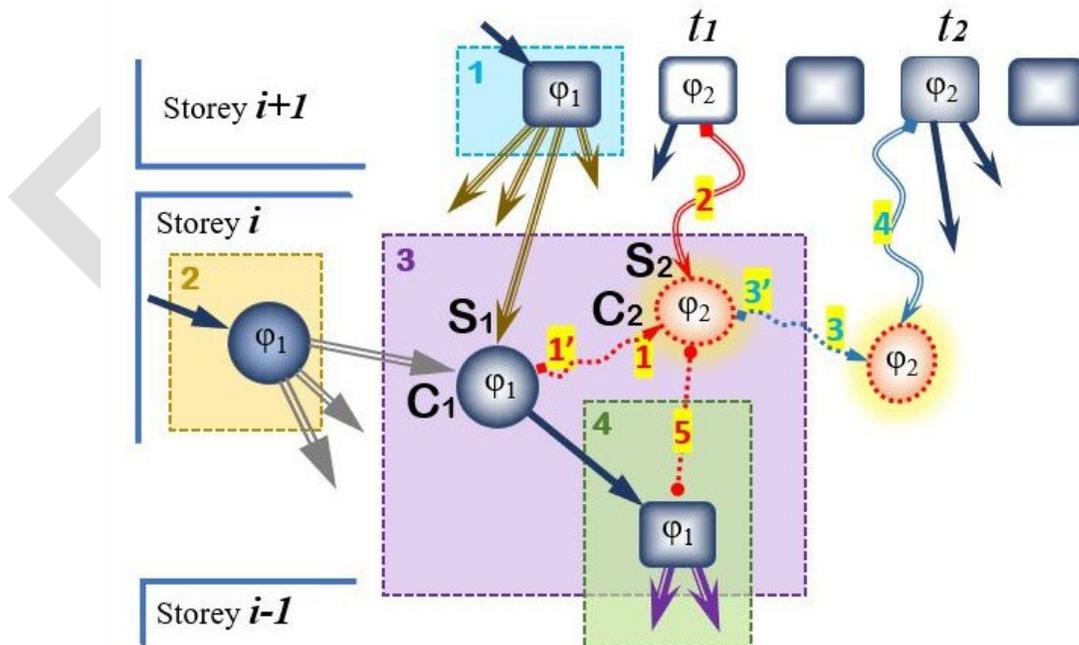
4.1 Add-on cells

Although the neurobiological terminology was not previously applied to GP processing units, a first function-to-structure attempt consists in mapping a GP unit onto a neuron-like cell. In this way, every time a given sequence is replayed by *Hp* across simulated offline computer sessions, its Cx private path gets fluently activated unless an unexpected stimulus occurs that triggers the sprouting of a new branch (i.e.: differentiation). Next repetitions of the same sequence add a new “formal neuron” to complete the same branch under construction. During the SWS phase, a replay cycle produces one pattern after the other at a high rate. The greater the number of patterns, the longer the timespan between two repetitions of the same pattern, although, neurites extension cannot be expected to follow the rate of subsequent replays. Molecular insights on the brain development and repair may shed light on this issue.

Inner processes called for repairing injuries of the nervous system such as stroke (Carmichael, 2017) or those implied by rewiring experiments in the visual cortex (Majewska and Sur, 2006), must face a similar situation to the updating of a GP path, namely to fill the gap between two distant units *A* and *B* that were/are coactive. For regeneration purpose, glial cells are shown to acquire a bipolar morphology and together form a bridge which guides axonal sprouting from *A* to *B* (Rigby et al, 2020). Not only do glial cells show the way owing to their orientation, but they also express *guidance cues* able to bind receptors present in the *growth cone* at the axon tip (Dominguez-Romero and Slater, 2021). Surprisingly few canonical molecules have been identified as *attractant/repellant* cues in animal species with a brain, be it damaged or not. Genetically-planned contributions of a few cues to the brain development hardly account for its high connectivity. Although the consequent difficulty for each brain axon to reach the proper target cells is widely acknowledged, most scientific reviews overlook ionic guidance cues (Stoeckli, 2018). Yet, the Ca^{2+} calcium ion can again be brought into play. Depending on whether Ca^{2+} is expressed at a low or high range inside the growth cone of an axon, the latter either expands forward or retracts (Henley and Poo, 2004). Among various directions to be taken by the *A* axon, this property signifies a trend to follow the one satisfying the highest Ca^{2+} concentration, notably favoured by calcium entry from extracellular source (Sutherland et al, 2014). Additionally, even apart from pathologies inducing their bridge-like aggregation, interstitial glial cells (i.e.: *microglia*) regulate neurogenesis and brain development in neurons still devoid of synapses, likely “*assisting activity-dependent neuronal integration*” (Cserép, 2022). Because *astrocytes* can convey intercellular Ca^{2+} waves over long distances in response to stimulation, glial cells can be suspected to form a *gradient tunnel*, reminiscent of NSC migration (Kaneko et al., 2017), between the *A* axon cone and a *B* dendrite. Calcium signals are indeed evoked by neuronal activity within glial cells, generate a spreading intercellular Ca^{2+} wave, and initiate responses in adjacent neurons (Deitmer et al, 1998). Given its particular dual sensitivity to calcium levels, the *A* cone thus likely expands in the direction that ensures the highest calcium, and retracts otherwise, when its intracellular Ca^{2+} does not receive a significant external input. Additionally, the parallel

pathfinding of nearby axons requires to be specified for each of them, besides the availability of a few chemical cues. Following a coding principle exploited here for STM, distinct phases/frequencies could distinguish concurrent waves of calcium spikes and therefore avoid mutual interference. At the molecular level, another major second messenger known as cyclic AMP (cAMP) participates in the local production of brief Ca^{2+} transients in the cone extensions, allowing “different downstream effectors to be sensitive to different frequencies” (Nicol et al, 2011) while steering the axon (Forbes et al, 2012). On the other side of *A-B* junction, at dendrites of *B* cell, the local generation of Ca^{2+} spikes (width < 20 ms) has recently been uncovered in layers 2/3 of the human cortex (Gidon et al., 2020) and rat hippocampus CA3, and assumed to “actively produce non-bursting, regular spiking firing phenotype” (Magó et al, 2021). Unlike the GP Differentiation routine in which the sprouting of a path cannot proceed before the completion of its previous section, synchronous phase-coding could thus be triggered by a given replay, and maintained until involved neurites that share the same frequency/phase (φ_1, φ_2 , in Fig. 8) form synapse. Because of the limited growth rate of axons, large spikes embedded into calcium waves should result in activation sustained long enough in order for the *A-B* distance to be covered, a process reminiscent of the long-term potentiation/depression (LTP/D) usually restricted to the setting of synaptic weights. Interestingly, high-amplitude Ca^{2+} triggers attractive steering of the cone and also induces LTP, whereas its low-amplitude Ca^{2+} is involved in both repulsive effect and LTD (Henley and Poo, 2011), implying that similar regulations could affect both axon outgrowth and subsequent synapse setting. According to the offline learning script advanced here, such pathfinding-oriented LTP/D should be hosted by the slow-wave fractions of 1½-hour sleep cycles. Given the average neurites growth rate that can be estimated around 50 $\mu\text{m}/\text{h}$, one cycle would therefore enable at most 75 μm of axon elongation, albeit for as many parallel axons as distinct Ca^{2+} “carrier waves” spreading in parallel. Is it by chance that stereotypic calcium waves named “glissandi” have been found to travel in synchrony over long distances in the cortex from one astrocyte to the other, while neuronal activity is reduced (Kuga et al., 2011) consistently with the GP learning constraint?

Add-on GP cells and connections



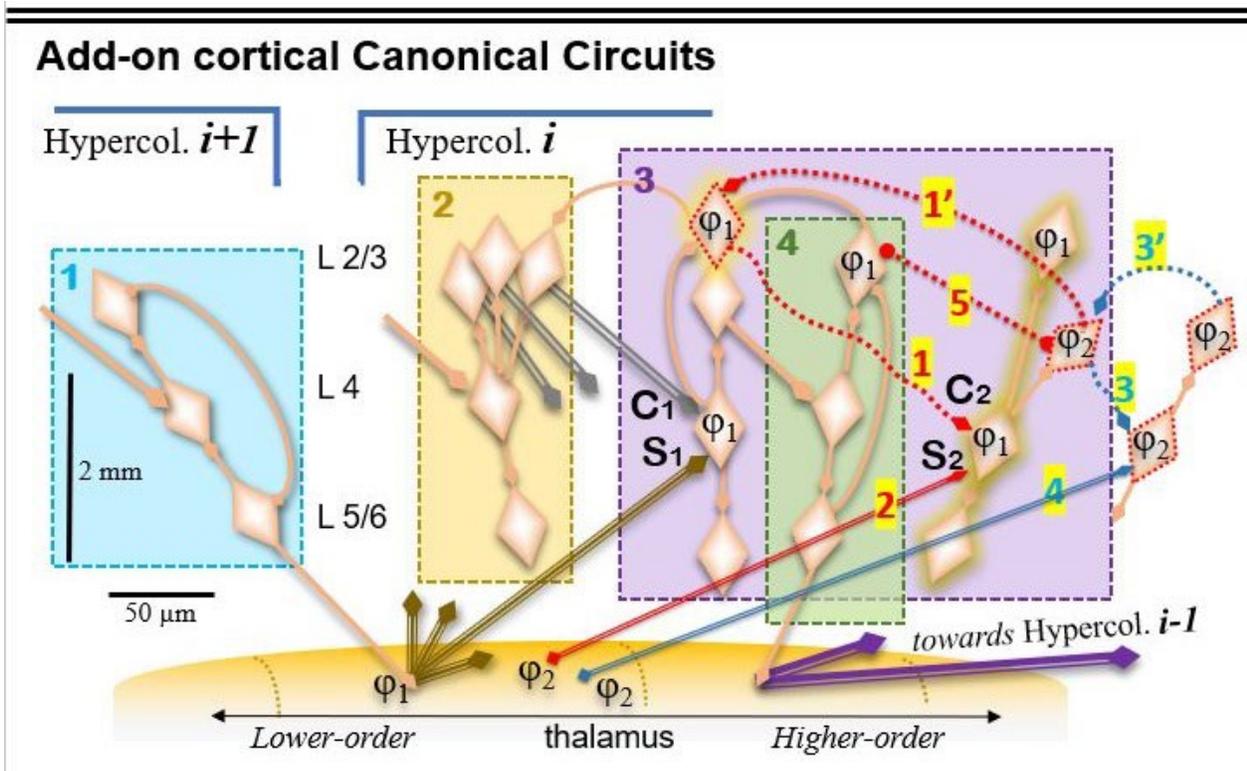


Figure 8. Tentative mapping of the GP topology (figure half-top in black and white) onto neural structures (figure half-bottom in skin tone). In both representations are add-on elements drawn with dotted pens. The characteristic Contextual (C) and Stimulus (S) inputs to processing units are emphasized. Proper connections are assumed to result from persistent synchronous signalling (e.g.: ϕ_1 , ϕ_2) shared by stimuli (blue box 1) and their respective target units (purple box 3). Each GP cell in the top window compares to a CC radial structure with prewired connections and free neurons in its layer-2 that can be specified (ϕ_2 for the add-on cell here), among other layers (L 2/3, L 4, L 5/6). Novel connections between CCs are those presumably created during HP offline replay from L2 add-on neurons to L4 of distant free CCs, whereas double lines represent the thalamocortical wiring. Crosstalk between hypercolumns akin to GP modules is mediated by distinct thalamic territories (displayed at the bottom). Whereas both upstream facilitation and downstream activity are plotted by a single sign (downstream arrow) in the GP display, they are identified by two separate arrows between CCs (activation labelled 1, 2...; facilitation labelled 1', 2'...).

4.2 Add-on groups of cells

“Economy of wiring” has been a leading concept in the search for very local groups of cells in the cortex (Hubel and Wiesel, 1962). The human cerebral cortex is on average 2.5 mm thick, with regional variations ranging from 1 to 4.5 mm (Fischl and Dale, 2000). Perpendicular to the layers of the cortex, the near-cylindrical structure known as *cortical column* can be regarded as a sort of toolbox the essential attributes of which are geared to the demands of a specific cortical area. This non-systematic view has infused the more recent notion of “*canonical circuit*” (Douglas and Martin, 1991), referred to in the following as CC (which stands for “cortical column” as well). CC variations span over the distribution of different cell types, the layers thickness, receptive fields properties, while the core circuitry notably controls the stimuli income and the excitation/inhibition balance (da Costa and Douglas, 2010). Of special interest here is the integration by CCs layer IV of two inputs, one issued from *thalamic* stimuli, the other one coming from layers 2/3 of another CC. A parallel can consequently be drawn with the dual input of a GP unit, whereby the latter can be activated by 1/ an upstream unit of the same storey and 2/ stimuli

from an upper, more peripheral storey. Mutual inhibition, as implemented between GP units primarily for resetting lapsed anticipations, involves inhibitory layer 2/3 interneurons across CCs (Helmstaedter, 2009). The neuroscientist who discovered cortical columns left half-open the question of their remote interactions by eventually stating that “*Columns in cytoarchitectural areas located at some distance from one another, but with some common properties, may be linked by long-range, intracortical connections.*” (Mountcastle, 1997). A more specific organization principle emerged from psycholinguistic considerations, such as priming effects in the treatment of sequences, suggesting a way for columns to anticipate thalamic stimuli. A primed/called column would seek to integrate an expected stimulus, hence the notion of “call-tree” at the core of a cortical model (Burnod, 1988; Alexandre et al., 1994). Quite relevant here, a call-tree resembles a GP module grown from several episodes of “learning by differentiation” wherein add-on units stand for as many CCs. Once acknowledged this relationship, checking the plausibility of layer-2 immature cells being integrated into the existing set of CCs fosters further anatomical review.

Cells of layer 5/6 are reciprocally connected to the Thalamus, whose primary role of transmitting sensory signals has been extended to relaying information across cortical regions (Sherman, 2017; Nakajima and Halassa, 2017). Similarly, the last GP-cell of a sprouting path, previously named Pattern Detector/Generator, stands at the interface with the next deeper storey, not only at the sensory ground-level but also through adjacent storeys that represent nesting levels of hierarchized patterns. Incidentally, a GP module is dedicated to treat a certain cluster of stimuli, which corresponds to the definition of a “*hypercolumn*”. Given that all PDGs undergo the same cyclic neuromodulation for learning purpose, it can be beneficial to let them interacting within the same structure that recalls the thalamus “hub”. In raising this analogy, the last unit of a memory path could project its stimulating output towards distant CCs within the next deeper storey, via a thalamus-like region. Consequently, the GP building becomes flattened, forming a mosaic of CC-like structures nested into hypercolumns, in relationship with inner stimuli of various levels, whilst keeping its original topology (Fig. 8). Of note, GP coincidence-detectors and detector/effectors can respectively correspond to distinct types of CCs. There are pre-wired mandatory connections in CCs. Four months are required for thalamocortical axons to develop in the human brain (Željka, 2017), which leads to suppose that limited neurites extension occurs for adaptive purpose from the adult thalamus. In Fig. 8, the S input to a layer-4 cell would therefore selectively consolidate one connection among many already present. But with respect to the C input, a specific new cross-connection between CCs can be envisioned. The thickness of a CC being at most the order of 25-30 μm (DaCosta and Martin, 2010), this is also the distance separating two neurons located along the central axis of their respective adjacent CCs. Provided that an axon can gain 75 μm during a sleep cycle, it may be able during this time interval to cross over one column for reaching its target CC. Five cycles would allow 375 μm of axon elongation, which means a distance of at most 12 CCs to be crossed by the origin layer-2 cell axon in order to find a free CC layer-4 cell in its surroundings. Although favourable, this result does not account for the distance between layer 2/3 and layer 4 which might also be travelled by the axon. This global calculation implies that the development of downstream/cross connections from a given CC would first enlist adjacent CCs. In the adult cortex, layer-2 NSCs could therefore only plug in the remaining free CCs, behind the full set of those successfully targeted by 3rd layer neurons at an early stage. Indeed, either short or long-distance connections likely depend on the originating layer, either 3rd or 2nd one (Vasković, 2023). The consequent learning-dependent disparity could explain the non-systematic distribution of responsive CCs that bewildered its supportive scientists. By implication, the older the adult cortex, the more distant the CCs that are not already used, the fewer the new connections possibly

built overnight, the longer the storage of a given memory, unless adult neurogenesis compensates for free-CCs depletion.

4.3 Neurobiological utterance of the GP learning algorithm

Expressing the offline growth of GP memory paths may now be permitted to borrow some wording from neurobiology. During sleep, axonal sprouting from layer-2 “dormant neurons” would allow cross-linkages of cortical CCs, steered in parallel by distinct Ca^{2+} waves, respectively stimulated by trajectory events rehearsed one after the other by HP. By referring to GP learning mechanisms, the thalamocortical signalling could for instance ensure the detection of unexpected thalamic activity thanks to the absence of cortical ‘reset’ feedbacks when a (thalamic) stimulus and (cortical) contextual signals fail to coincide. Unexpected stimuli remain active, which make them respond to a regular depolarizing signal in a learning situation. Provided an available “carrier wave”, differentiation can begin. An extra branch (C) sprouts from the last fully activated CC towards a free CC that also becomes the target of the unexpected thalamic output tuned to the same wave. This would be compatible with an “instructive” role of the thalamus, even “*in late network development that persist into adulthood as substrate for learning and memory*” (Sur and Leamey, 2001). Blind axonal extension along a preferred direction, repelled by concurrent travelling waves, attracted by free CCS (e.g.: chemical attractants or Ca^{2+} wave concurrently brought by thalamic afference), may channel this search likely driven by the cortical spontaneous activity. Nevertheless, whether the development of cortical maps is driven by the inner neural activity or its periphery still remains an elusive issue (López-Bendito, 2018), and justifies modelling to be brought into play for testing relevant hypotheses (Fig. 9).

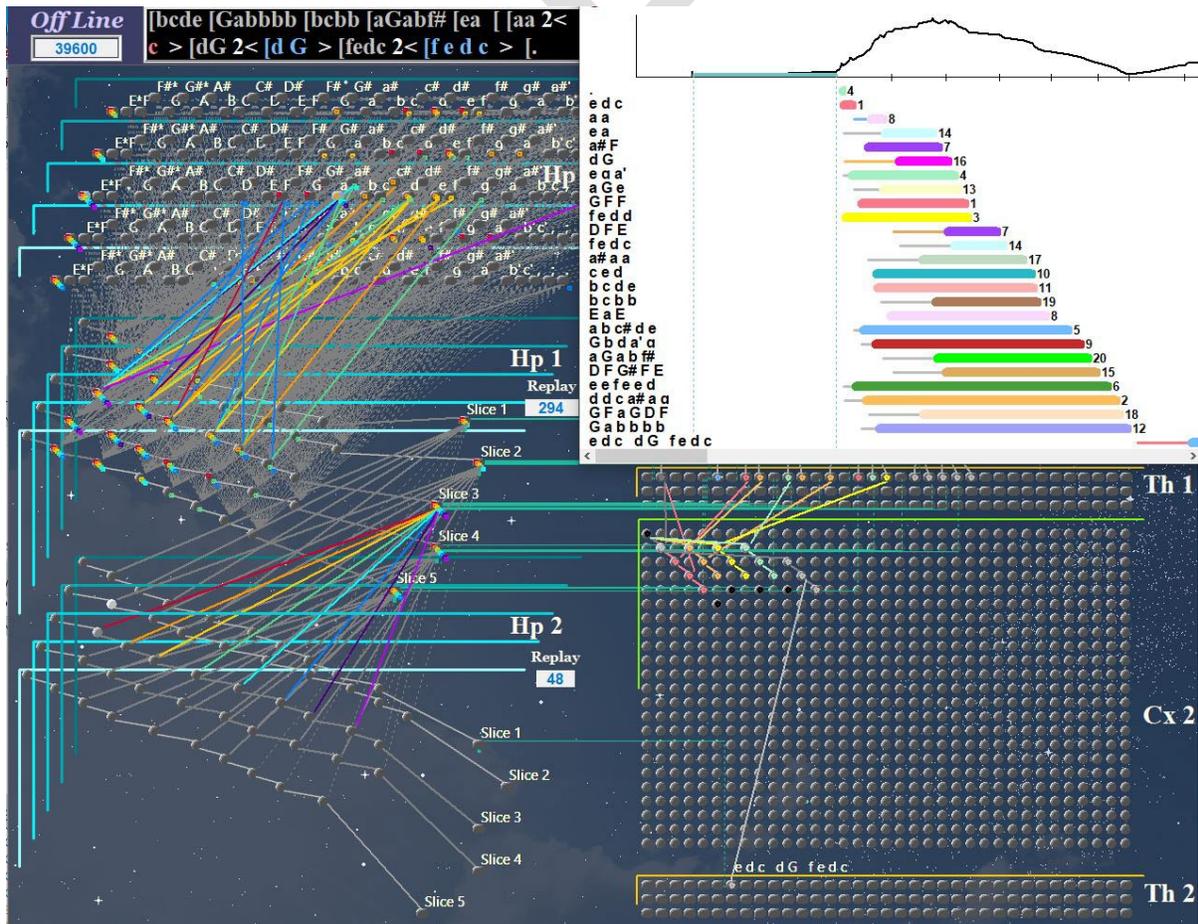


Figure 9. Offline parallel growth of GP memory paths when carried by distinct waves within a matrix of *Cx* units akin to cortical canonical circuits. To the right-hand side, 5 *Hp* slices alternatively broadcast the 5 trajectories they have encoded in *Hp2* (storey -2) towards *Cx* (to the right-hand side). The resulting simultaneous extension of up to 20 paths in the Storey -1 *Cx1* (hidden here by a pop-up window) benefits from as many carrier waves (identified here by distinct colours). Free units can smoothly be targeted at the beginning of encoding, when the matrix is only partly mapped onto trajectory events. As learning proceeds, every completed path connects to its associated *Hp* generic path which can be released of its ongoing phasic codes. The next online period will in this manner be able to use the same recycled phases. The *Cx* path carrier-wave is also freed, allowing its new use for accompanying another path in its growth. This screenshot was taken after the completion of *Cx1* paths. The 2nd storey is in turn busy encoding full compound trajectories as they are replayed by *Hp*. Among the 5 relevant paths that are currently built in Storey -2, one has just been finished, and therefore has received a label made from concatenating its 'component units' labels. Every such label appears in the top-right window to the left of thick coloured lines that last as long as the sprouting of the path they represent.

According to the above, forming new cortical memory paths can be impaired by several factors, including the growing scarcity of CCs at disposal, and the recycling of distinct carrier waves. In the computer experiments reported in Fig. 10, the LTM completion date is delayed by the scarcity of available waves (i.e.: software) accompanying a sort of 'hardware upgrading'. From a medical point of view to be considered in future GP developments, consequences on memory performance of offline replays interruptions will notably be viewed against sleep apnea symptoms.

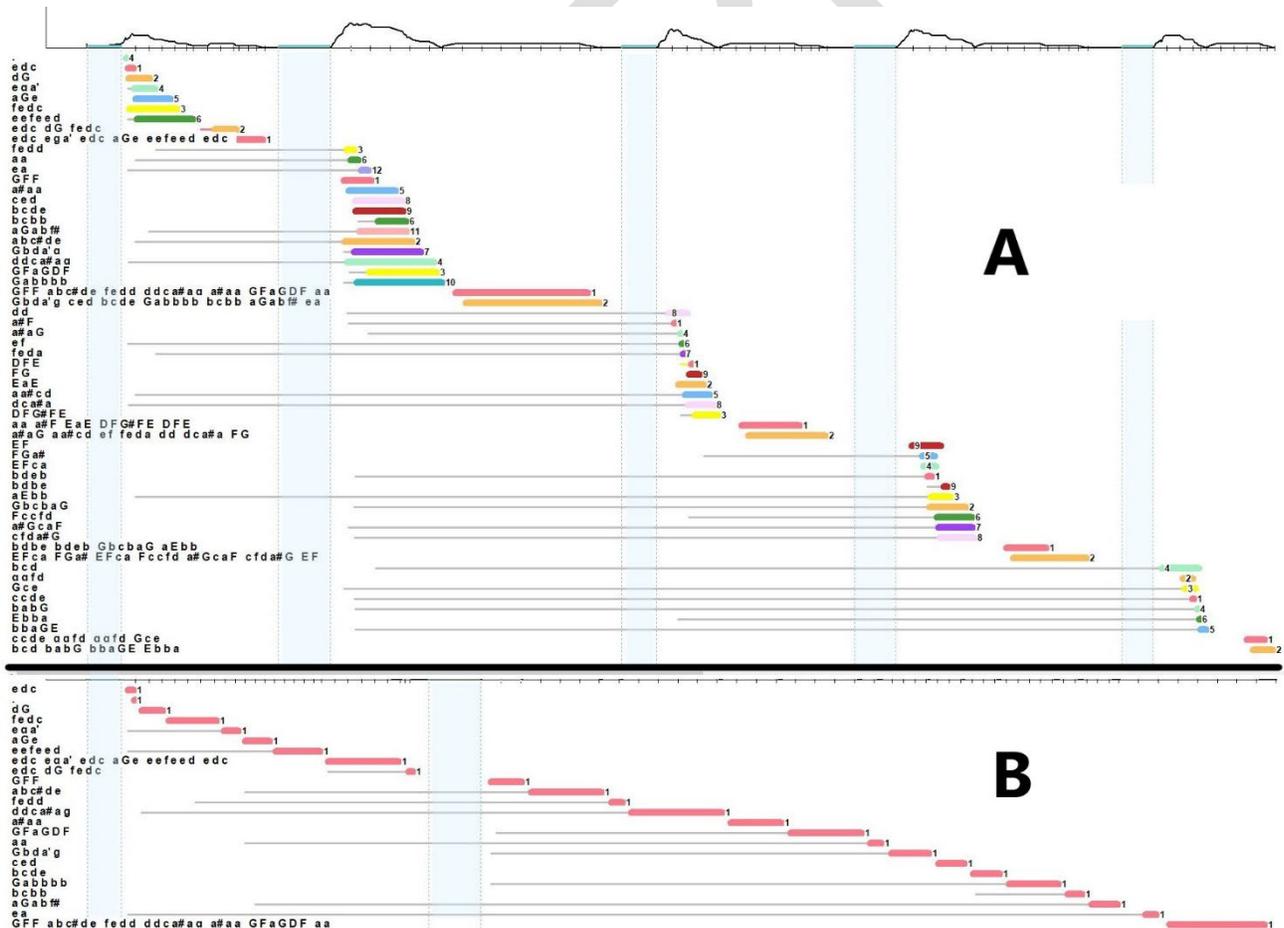


Figure 10. Either parallel (**A**) or serial (**B**) treatment by *Cx* of a *Hp* replay session. In both cases, *Hp* contains here two active slices, and can thus encode two complex trajectories during online phases. **A**: Offline, the formation of memory paths in parallel streams is based on the generation of a new carrier wave whenever *Cx* sprouts a new branch (Differentiation), as long as a free wave is available. The curve at the top tells how many waves are dynamically brought into play, with each mark along the time-axis stating when a replay cycle is launched by *Hp2*. **B**: With only one available wave, the same process stays serial, and its duration is significantly stretched: here, once the parallel process is completed, 2/3 of trajectories still remain to be encoded through the serial way.

5. Conclusion

If the neurobiological basis of learning and memory has hitherto been dominated by studies focusing on the hippocampus, it also appears that neocortical contributions to learning cannot be considered without involving the thalamic crossroads between brain regions. Likewise, regarding memory-oriented interactions between HP and the cortex, a distinction must be drawn between sleep and waking phases, for in particular last decades studies have assigned sleep to information transfer from hippocampal to cortical storage. But among several simultaneous HP and cortical electrical oscillations, the right moment for this transfer, as well as the leadership and driving influences between HP, cortex and thalamus remains a matter of controversy. The earlier is usually considered the leader. But watching brain electrical activities during replay pertains to listening to a radio symphony broadcast without knowing neither musical score nor conductor gesture meant to pace the instruments. The ‘conducting neuromodulation’ cannot be directly captured, apart maybe from recent calcium imaging facilities. By contrast, the memory model used here includes viewable modulating signals, notably essential to carry out “replay”. Triggering modulation signals that spread in parallel can precede local activations planned and completed in a certain order by a central device, not necessarily due to some cross-control between the involved players such as HP and cortex.

Elements of essential communication have however been enhanced here between *Hp* and *Cx*, representing respectively HP and a cortical channel in the GP framework. Online, since only relevant (i.e.: novel and emotionally strong) information deserves being learnt, currently existing *Cx* memory paths transmit their activation to *Hp* in order to prevent the useless phasic encoding of already known events. Online as well, a process – not simulated yet with GP – would conversely allow *Hp* to repetitively generate STM trajectories aimed at coinciding with ongoing events while rehearsing a given behaviour. Offline, *Hp* replay of a given STM trajectory can stop when its LTM *Cx* path is completed, which is notified via a *Cx-Hp* new cross-connection created between the tips of the *Hp* and new *Cx* memory paths. Interestingly, this cross linkage requires coincident activations between its origin and destination; the new *Cx* memory path must therefore be played for slightly later activating its *Hp* partner offline. Learning by coincidence-detection in the case of *Cx-Hp* connections thus raises the assumption that dreams could be a side-effect of building circuits required for serving the *Hp-Cx* collaboration. These cross-circuits will notably allow a ‘replaying’ *Hp* generic path to know when all its phasic patterns have been translated into distinct *Cx* paths within a storey. Computer simulations showed that this last suggestion of *Cx-Hp* interaction determines the growth of higher-level paths within a deeper storey.

The cooperative model presented here provides an example of how neural codes (tonic, phasic) and processes (coincidence detection, replay, neuromodulation) can together contribute to transform new episodic memories - supposedly recorded by the hippocampus - into cortical permanent traces through both recruitment of free ‘canonical circuits’ and recyclable characteristic waves. Because this procedure is disturbed while neuromodulation favours inner predictive

signals, offline periods analogous to sleep are mandatory. More broadly, the notion of “offline cortical sprouting for learning purpose”, although untested yet, is bound to a series of embedded prerequisites that find true implementations in the brain: the proper growth of GP memory path needs the type of modulation/segregation associated with sleep, which then requires a recorder/player device to memorize online experience to be replayed offline, which necessitates rapid encoding as supplied by HP phasic signalling.

A main outcome of this view is certainly the unexpected discovery of some functional matching between GP units and cortical columns, as well as between GP modules and hyper-columns. In the end, the expression “guided propagation” may reflect the way hyper-column spontaneous activity could be steered by thalamic stimuli and modulating signals, sometimes under the only HP replaying skill. In other respects, that add-on circuits could participate in the lifelong adaptive play invites to reassess once more the blurry frontier between the brain structures that are mainly issued from predefined genetic programs and those that are shaped during adulthood by the unforeseeable environment, presumably thanks to hippo-cortical collaboration.

Abbreviations

ANN: Artificial neural network; Ca²⁺ calcium ion; CC: Canonical Circuit / Cortical Column; CDU: Context-Dependent Unit; DCX+: doublecortin marker of immaturity; EEG: Electroencephalogram; GP: Guided propagation; HP: Hippocampus; RPI: Reference Phasic Interval; LFP: Local field potential; LTM: Long-term memory; LTP/D: Long-Term Potentiation/Depression; Hp: GP representation of HP; Cx: GP representation of Cortex area; NSC: Neural stem cells; PDG: Pattern detector/generator; PS: Paradoxical sleep; REM: Rapid eyes movements; SPW-R: Sharp wave ripple; STM: Short-term memory; SWS: Slow wave sleep

References

- Abadchi, J.K. et al (2020) Spatiotemporal patterns of neocortical activity around hippocampal sharp-wave ripples, *eLife* 9:e51972. doi: 10.7554/eLife.51972
- Abraham, W. C., & Robins, A. (2005) Memory retention - the synaptic stability versus plasticity dilemma. *Trends in neurosciences*, 28(2), 73–78. doi: 10.1016/j.tins.2004.12.003
- Ackermann, S., & Rasch, B. (2014). Differential effects of non-REM and REM sleep on memory consolidation? *Current neurology and neuroscience reports*, 14(2), 430. <https://doi.org/10.1007/s11910-013-0430-8>
- Aimone, J.B. (2016) Computational Modeling of Adult Neurogenesis, *Cold Spring Harb Perspect Biol* 8:a018960, doi: 10.1101/cshperspect.a018960
- Alexandre, F., Guyot, F., Haton, J.-P., Burnod, Y. (1991) The cortical column: A new processing unit for multilayered networks, *Neural Networks* 4(1):15-25. doi:10.1016/0893-6080(91)90027-3
- Altman, J. (1962) Are new neurons formed in the brain of adult mammals? *Science* 135, 1127-1128. doi: 10.1126/science.135.3509.1127
- Antony, J.W., Schönauer, M., Staresina, B.P., Cairney, S.A. (2019) Sleep Spindles and Memory Reprocessing. *Trends Neurosci.* 42(1):1-3. doi: 10.1016/j.tins.2018.09.012.

- Andrillon, T., Nir, Y., Staba, R.J., Ferrarelli, F., Cirelli, C., Tononi, G., Fried, I. (2011) Sleep spindles in humans: insights from intracranial EEG and unit recordings, *J Neurosci* 7;31(49):17821-34, doi: 10.1523/JNEUROSCI.2604-11.2011
- Aquino, J.B. et al (2012) Positional differences of axon growth rates between sensory neurons encoded by Runx3. *EMBO J.* 12;31(18):3718-29. doi: 10.1038/emboj.2012.228.
- Barnes, D.C., Wilson D.A. (2014) Sleep and olfactory cortical plasticity, *Frontiers in Behavioral Neuroscience* 8, doi:10.3389/fnbeh.2014.00134
- Berdugo-Vega, G., Lee, C-C., Garthe, A., Kempermann, G., Calegari, F. (2021) Adult-born neurons promote cognitive flexibility by improving memory precision and indexing, *Hippocampus*, 31:10,1068-1079, doi: 10.1002/hipo.23373
- Béroule, D. (1989) The Never-Ending Learning. In: Eckmiller, R., v.d. Malsburg, C. (eds) *Neural Computers*. Springer Study Edition, vol 41. Springer, Berlin, Heidelberg. doi:10.1007/978-3-642-83740-1_24
- Béroule, D. (2004) An instance of coincidence detection architecture relying on temporal coding. *IEEE Trans. Neural Netw.* In: DeLiang W, et al. editors. Special issue on temporal coding for neural information processing, 15(5):963–979. doi: 10.1109/TNN.2004.833137.
- Béroule, D., Gisquet-Verrier P. (2016) A functional model of fast action selection guided by emotional stimuli. *Int J Swarm Intel Evol Comput.* 5(132):2. doi: 10.4172/2090-4908.1000132
- Béroule, D.G. (2016) Encoding of memory across online/offline alternations. Screencast of running computer simulation. https://perso.limsi.fr/domi/Movie-S1_DGB_nov16.mov.
- Béroule, D. G. (2018) Offline encoding impaired by epigenetic regulations of monoamines in the guided propagation model of autism. *BMC neuroscience*, 19(1), 80. <https://doi.org/10.1186/s12868-018-0477-1>
- Béroule, D. G. (2023) Memory-oriented cooperation between brain devices across sleep-wake cycles. https://perso.limsi.fr/domi/Sleep-Memory-GPS_2023.mov
- Bhardwaj, R.D., Curtis, M.A., Spalding, K.L. et al (2006) From the Cover: Neocortical neurogenesis in humans is restricted to development, *Proceedings of the National Academy of Sciences* 103(33):12564-8. doi: 10.1073/pnas.0605177103
- Blanchet, P. (1994). An Architecture for Representing and Learning Behaviors. In *From Animals to Animals 3: Proceedings of the Third International Conference on Simulation of Adaptive Behavior*, Vol. 3, MIT Press, 334-344. ISBN: 9780262531221
- Bliss, T. V., and Gardner-Medwin, A. R. (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the unanaesthetised rabbit following stimulation of the perforant path. *The Journal of physiology*, 232(2):357–374. doi: 10.1113/jphysiol.1973.sp010274
- Bonfanti, L, Nacher, J. (2012) New scenarios for neuronal structural plasticity in non-neurogenic brain parenchyma: the case of cortical layer II immature neurons. *Progress in Neurobiology* 98:1–15. doi:[10.1016/j.pneurobio.2012.05.002](https://doi.org/10.1016/j.pneurobio.2012.05.002)
- Born, J., Wilhelm, I. (2012) System consolidation of memory during sleep. *Psychol Res.* 76(2):192-203. doi: 10.1007/s00426-011-0335-6.
- Brown, R.E., Basheer, R., McKenna, J.T., Strecker, R.E., and McCarley, R.W. (2012) Control of sleep and wakefulness, *Physiol Rev* 92:1087-187. doi: 10.1152/physrev.00032.2011

- Brownell, W.E. (1990) Outer hair cell electromotility and otoacoustic emissions. *Ear Hear.* Apr;11(2):82-92. doi: 10.1097/00003446-199004000-00003.
- Buhry, L., Azizi, A.H., and Cheng, S. (2011) Reactivation, Replay, and Preplay: How it Might All Fit Together, *Neural Plasticity* 2011 203462, 11 pages, doi: 10.1155/2011/203462
- Burnod, Y. (1988) *An Adaptive neural network: the cerebral cortex*, Ed. Masson, 367 p, ISBN: 978-2-225-81538-6
- Bush, D., and Burgess, N. (2019) Neural Oscillations: Phase Coding in the Absence of Rhythmicity, *Current Biology* 29(R50-R70), doi: 10.1016/j.cub.2018.11.056
- Buzsáki, G. (1989) Two-stage model of memory trace formation: a role for “noisy” brain states, *Neuroscience* 31:551-570. doi: 10.1016/0306-4522(89)90423-5
- Buzsáki, G. (1998) Memory consolidation during sleep: a neurophysiological perspective. *J Sleep Res.* 7(1):17–23. doi: doi: 10.1046/j.1365-2869.7.s1.3.x.
- Buzsáki, G., Lopes da Silva, F.L. (2012) High frequency oscillations in the intact brain, *Prog Neurobiol.* 98(3): 241-249. doi: 10.1016/j.pneurobio.2012.02.004
- Buzsáki, G. (2015) Hippocampal Sharp wave-ripple: a cognitive biomarker for episodic memory and planning. *Hippocampus* 25:1073-1188. doi: 10.1002/hipo.22488.
- Cantero, J.L., Atienza, M., Stickgold, R., et al. (2003). Sleep-dependent theta oscillations in the human hippocampus and neocortex. *J. Neurosci.* 23(34):10897-903. doi: 10.1523/JNEUROSCI.23-34-10897.2003.
- Carmichael, S. T., Kathirvelu, B., Schweppe, C. A., & Nie, E. H. (2017) Molecular, cellular and functional events in axonal sprouting after stroke. *Experimental neurology*, 287(Pt 3), 384–394. doi: 10.1016/j.expneurol.2016.02.007
- Chen, Z. and Liu, B. (2018) Continual Learning and Catastrophic Forgetting, in “Lifelong Machine Learning”, Morgan & Claypool Publishers, 55-75. doi: 10.1007/978-3-031-01581-6_4
- Cipolli, C, Ferrara M, De Gennaro L, Plazzi G (2017) Beyond the neuropsychology of dreaming: Insights into the neural basis of dreaming with new techniques of sleep recording and analysis, *Sleep Medicine Reviews* 35, 8-20, 35:8-20. doi: 10.1016/j.smr.2016.07.005
- Clemens, Z, Mölle M, Eröss L, Barsi P, Halasz P and Born J (2007) Temporal coupling of parahippocampal ripples, sleep spindles and slow oscillations in humans, *Brain* 130(11):2868-78. doi: 10.1093/brain/awm146
- Clouter, A., Shapiro, K L, Hansimayr, S. (2017) Theta Phase Synchronization is the Glue that Binds Human Associative Memory, *Current Biology* 27, 3143-3148. doi: 10.1016/J.cub.2017.09.001
- Colangelo, A.M., Cirillo, G., Alberghina, L., Papa, M., Westerhoff, H.V. (2019) Neural plasticity and adult neurogenesis: the deep biology perspective, *Neural Regen Res* 14(2):201-205. doi: 10.4103/1673-5374.244775.
- Colonesse, M.T., Phillips, M.A. (2018) Thalamocortical function in developing sensory circuits, *Current Opinion in Neurobiology* 52, 72-79, doi: 10.1016/j.conb.04.019
- Cooper, N.P., Guinan, J.J. Jr (2006) Efferent-mediated control of basilar membrane motion. *J Physiol* 576: 49–54.

- Cserép, C., Schwarcz, A.D., Pósfai, B., László, Z.I., Kellermayer, A., Környei, Z., Kisfali, M., Nyerges, M., Lele, Z., Katona, I., and Dénes, A. (2022) Microglial control of neuronal development via somatic purinergic junctions. *Cell reports*, 40(12):111369, doi: 10.1016/j.celrep.2022.111369
- Da Costa, N. M., & Martin, K. A. (2010) Whose Cortical Column Would that Be?. *Frontiers in neuroanatomy* 4(16). doi: 10.3389/fnana.2010.00016
- D’Arcangelo, G. (2014) Reelin in the years: Controlling Neuronal Migration and Maturation in the Mammalian Brain, *Advances in Neuroscience 2014*, ID 597395, 19p. doi: [10.1155/2014/597395](https://doi.org/10.1155/2014/597395)
- Deitmer, J. W., Verkhratsky, A. J., & Lohr, C. (1998) Calcium signalling in glial cells. *Cell calcium*, 24(5-6):405–416. doi: 10.1016/s0143-4160(98)90063-x
- Devreotes, P., and Horwitz, A.R. (2015) Signaling Networks that Regulate Cell Migration, *Cold Spring Harb Perspect Biol* 7:a005959, doi: 10.1101/cshperspect.a005959
- Diba, K., and Buzsáki, G. (2007) Forward and reverse hippocampal place-cell sequences during ripples, *Nat Neurosci.* 10(10): 1241-1242
- Diekelmann, S, Born J. (2010) The memory function of sleep. *Nat Rev Neurosci.* 11(2):114-26. doi: 10.1038/nrn2762.
- Domínguez-Romero, M. E., & Slater, P. G. (2021) Unraveling Axon Guidance during Axotomy and Regeneration. *International journal of molecular sciences*, 22(15), 8344. doi:10.3390/ijms22158344
- Douglas, R. J., and Martin, K. A. (1991) A functional microcircuit for cat visual cortex. *The Journal of physiology* 440:735–769. Doi: 10.1113/jphysiol.1991.sp018733
- Draganski, B., Gaser, C., Kempermann, G., Kuhn, H.G., Winkler, J., Büchel, C., May, A. (2006) Temporal and Spatial Dynamics of Brain Structure Changes during Extensive Learning, *Journal of Neuroscience* 26 (23) 6314-6317, doi: 10.1523/JNEUROSCI.4628-05.2006
- Dragoi, G., Tonegawa, S. (2011) Preplay of future place cell sequences by hippocampal cellular assemblies. *Nature* 469, 397–401, doi:10.1038/nature09633
- Eichenbaum, H. (2013) Memory on time, *Trends in Cognitive Sciences* 17(2):81-88, doi:10.1016/j.tics.2012.12.007
- Eichenlaub et al (2020) Replay of Learned Neural Firing Sequences during Rest in Human Motor Cortex, *Cell Reports* 31, 107581. doi: 10.1016/j.celrep.2020.107581
- Ehninger, D., and Kempermann, G. (2008). Neurogenesis in the adult hippocampus. *Cell and tissue research*, 331(1), 243-250. doi:10.1007/s00441-007-0478-3
- Ernst, A., Alkass, K., Bernard, S. (2014) Neurogenesis in the Striatum of the Adult Human Brain, *Cell* 156:1072-1083. doi:10.1016/j.cell.2014.01.044
- Erwin, S.R., Sun, W., Copeland, M., Lindo, S., Spruston, N., and Cembrowski, M.S. (2020). A Sparse, Spatially Biased Subtype of Mature Granule Cell Dominates Recruitment in Hippocampal-Associated Behaviors. *Cell Rep.* 31, 107551. doi: 10.1016/j.celrep.2020.107551
- Euston, D.R., Tatsuno, M. McNaughton, B.L. (2007) Fast-Forward Playback of Recent Memory Sequences in Prefrontal Cortex During Sleep, *Science* 318, 1147-1150, doi: 10.1126/science.1148979

- Green, J. D., and Arduini, A. A. (1954). Hippocampal electrical activity in arousal. *J. Neurophysiol.* 17, 533-557. doi: 10.1152/jn.1954.17.6.533
- Ferrara, M., Moroni, F., De Gennaro L., and Nobili, L. (2012) Hippocampal sleep features: relations to human memory function, *Frontiers in Neurology* 3:57, doi: 10.3389/fneur.2012.00057
- Findlay, G., Tononi, G., and Chiara Cirelli, C. (2020) The evolving view of replay and its functions in wake and sleep, *Sleep Advances*, 2020, 1–14, doi: 10.1093/sleepadvances/zpab002
- Fischl, B. and Dale A.M. (2000) Measuring the thickness of the human cerebral cortex from magnetic resonance images, *PNAS* 97(20):11050-11055, doi: 10.1073/pnas.200033797
- Forbes, E. M., Thompson, A. W., Yuan, J., and Goodhill, G. J. (2012) Calcium and cAMP levels interact to determine attraction versus repulsion in axon guidance. *Neuron*, 74(3):490–503. Doi: 10.1016/j.neuron.2012.02.035
- Fuchs, E., and Flügge, G. (2014) Adult neuroplasticity: More Than 40 Years of Research, *Neural Plasticity* 2014, 10 pages, doi: 10.1155/2014/541870
- Gangarossa, G., Laffray, S., Bourinet, E. and Valjent, E. (2014) T-type calcium channel Cav3.2 deficient mice show elevated anxiety, impaired memory and reduced sensitivity to psychostimulants, *Front. Behav. Neurosci.* 8, doi : 10.3389/fnbeh.2014.00092
- Geva-Sagiv, M., & Nir, Y. (2019) Local Sleep Oscillations: Implications for Memory Consolidation. *Frontiers in neuroscience*, 13, 813. doi: 10.3389/fnins.2019.00813
- Gidon, A., Zolnik, T. A., Fidzinski, P., Bolduan, F., Papoutsi, A., Poirazi, P., Holtkamp, M., Vida, I., and Larkum, M. E. (2020) Dendritic action potentials and computation in human layer 2/3 cortical neurons. *Science* 367(6473): 83–87. doi: 10.1126/science.aax6239
- Gisquet-Verrier, P., Riccio, D. (2018) Memory integration: An alternative to the consolidation/reconsolidation hypothesis, *Progress in Neurobiology*, 171:15–31, doi: 10.1016/j.pneurobio.2018.10.002
- Giuditta, A. (2014) Sleep memory processing: the sequential hypothesis. *Frontiers in systems neuroscience*, 8, 219. <https://doi.org/10.3389/fnsys.2014.00219>
- Gonzalez-Perez, O. (2012) Neural stem cells in the adult human brain, *Biol Biomed Rep.* 2(1):59-69. PMID: 23181200.
- Haber, S. N., Fudge, J.L., McFarland, N.R. (2000) Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci.* 20(6):2369–82. doi: 10.1523/JNEUROSCI.20-06-02369.2000.
- Hafting, T., Fyhn, M., Bonnevie, T., Moser, M.-B., and Moser, E.I. (2008) Hippocampus-independent phase precession in entorhinal grid cells. *Nature* 453(7199):1248-52. doi: 10.1038/nature06957
- Hakim, N., Vogel, E.K. (2018) Phase-coding memories in mind, *Plos Biol* 16(8): e3000012. doi: 10.1371/journal.pbio.3000012
- Han, D.H., Park, P., Choi, D.I., Bliss, T.V.P., Kaang, B-K. (2021) The essence of engram: Cellular or synaptic?, *Seminars in Cell and Developmental Biology*, doi:10.1016/j.semcd.2021.05.033

- Hanna, R.J., Franck, L.M. (2018) The hippocampal sharp wave-ripple in memory retrieval for immediate use and consolidation, *Nat Rev Neurosci.* 19(12):744-757, doi: 10.1038/s41583-018-0077-1
- Hanslmayr, S., Staresina, B.P., and Bowman, H. (2016) Oscillations and Episodic Memory: Addressing the Synchronization/Desynchronization Conundrum, *Trends in Neuroscience*, 39:1, doi: 10.1016/j.tins.2015.11.004
- Hasselmo, M.E. (2005) What is the Function of Hippocampal Theta Rhythm? - Linking Behavioral Data to Phasic Properties of Field Potential and Unit Recording Data, *Hippocampus* 15, 936-949, doi: 10.1002/hipo.20116
- Heilfrich, R.F., Lender, J.D., Mander, B.A. et al (2019) Bidirectional prefrontal-hippocampal dynamics organize information transfer during sleep in humans, *Nature Communications* 10:3572, doi: 10.1038/s41467-019-11444-x
- Helmstaedter, M., Sakmann, B., and Feldmeyer, D. (2009) Neuronal correlates of local, lateral, and translaminar inhibition with reference to cortical columns. *Cerebral cortex (New York, N.Y.: 1991)*, 19(4):926–937. doi: 10.1093/cercor/bhn141
- Henley, J., & Poo, M. M. (2004) Guiding neuronal growth cones using Ca²⁺ signals. *Trends in cell biology*, 14(6):320–330. doi: 10.1016/j.tcb.2004.04.006
- Hubel, D.H., and Wiesel, T.N. (1962) Receptive fields, binocular interaction and functional architecture in the cat's visual cortex, *J.Physiol.* 160 :106-154
- Hwang, K., Bertolero, M.A., Liu, W.B., D'esposito, M. (2017) The Human Thalamus Is an Integrative Hub for Functional Brain Networks, *The Journal of Neuroscience*, 37(23):5594-5607. doi: 10.1523/JNEUROSCI.0067-17.2017
- Ji, D., Wilson, M.A. (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nat Neurosci.* 10(1):100-7. doi: 10.1038/nn1825.
- Jiang, X., Shamie, I., Doyle, W.K., et al (2017) Replay of large-scale spatio-temporal patterns from waking during subsequent NREM sleep in human cortex, *Scientific Reports* 7/17380. doi: 10.1038/s41598-017-17469-w
- Jiang, X., Gonzalez-Martinez, J., and Halgren, E. (2019) Posterior Hippocampal Spindle Ripples Co-occur with Neocortical Theta Bursts and Downstates-Upstates, and Phase-Lock with Parietal Spindles during NREM Sleep in Humans. *The Journal of neuroscience* 39(45) 8949–8968. doi:10.1523/JNEUROSCI.2858-18.2019
- Joo, H.R., Frank, L.M. (2018) The hippocampal sharp wave-ripple in memory retrieval for immediate use and consolidation, *Nat Rev Neurosci* 19(12): 744-757, doi: 10.1038/s41583-018-0077-1
- Josselyn, S.A., Tonegawa, S. (2020) Memory engrams: Recalling the past and imagining the future, *Science* 367(6473), doi:10.1126/science.aaw4325
- Jurkowski, M. P., Bettio, L., K Woo, E., Patten, A., Yau, S. Y., & Gil-Mohapel, J. (2020) Beyond the Hippocampus and the SVZ: Adult Neurogenesis Throughout the Brain. *Frontiers in cellular neuroscience*, 14, 576444. doi: 10.3389/fncel.2020.576444
- Kaneko, N., Sawada, M., and Sawamoto, K. (2017). Mechanisms of neuronal migration in the adult brain, *J. Neurochem.* 141:835-847. doi: 10.1111/jnc.14002

- Kempermann, G. (2020) Delayed gratification in the adult brain, *eLife* 9:e59786, doi: 10.7554/eLife.59786
- Klinzing, J. G., Niethard, N., & Born, J. (2019). Mechanisms of systems memory consolidation during sleep. *Nature neuroscience*, 22(10), 1598-1610. doi: 10.1038/s41593-019-0467-3
- König, R., Benedetti, B., Rotheneichner, P., O' Sullivan, A., Kreutzer, C., Belles, M., Nacher, J., Weiger, T.M., Aigner, L., Couillard-Després, S. (2016) Distribution and fate of DCX/PSA-NCAM expressing cells in the adult mammalian cortex: a local reservoir for adult cortical neuroplasticity? *Frontiers in Biology* 11:193–213. doi: 10.1007/s11515-016-1403-5
- Kuangpin, L., Ma, W., Li, C. (2020) Advances in transcription factors related to neuroglial cell reprogramming, *Translational Neuroscience* 11:17-27. doi:10.1515/tnsci-2020-0004
- Kuga, N., Sasaki, T., Takahara, Y., Matsuki, N., & Ikegaya, Y. (2011) Large-scale calcium waves traveling through astrocytic networks in vivo. *The Journal of neuroscience: the official journal of the Society for Neuroscience* 31(7), 2607–2614. doi: 10.1523/JNEUROSCI.5319-10.2011
- La Rosa, C., Cavallo, F., Pecora, A., Chincarini, M., Ala, U., Faulkes, C.G., Nacher, J., Cozzi, B., Sherwood, C., Amrein, I., Bonfanti, L. (2020) Phylogenetic variation in cortical layer II immature neuron reservoir of mammals, *eLife* 9 :e55456. doi: 10.7554/eLife.55456
- Landolt, H-P., and Holst, S.C. (2016) Ionic control of sleep and wakefulness, *Science*, 29 Apr 2016, 352(6285):517-518, doi: 10.1126/science.aaf8178
- Le Cun, Y. (1988) A Theoretical Framework for Back-Propagation, *Proceeds of the 1988 Connectionist Models Summer School*, 21-28. Corpus ID: 16775098
- Lee, A.K., Wilson, M.A. (2002) Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron* 36:1183–94. doi:10.1016/S0896-6273(02)01096-6
- Lee, J., Song, K., Lee, K., Hong, J., Lee, H., Chae, S., Cheong, E., Hee-Sup Shin, H.-S.(2013) Sleep spindles are generated in the absence of T-type calcium channel-mediated low-threshold burst firing of thalamocortical neurons, *PNAS* 110(50):20266-71, doi: 10.1073/pnas.1320572110
- Li, W., Ma, L., Yang, G., and Gan, W. (2017) REM sleep selectively prunes and maintains new synapses in development and learning, *Nat. Neurosci.* 20(3):427-437. doi:10.1038/nn.4479
- Lisman, J.E., Idiart, M.A.P. (1995) Storage of 7 +/-2 Short-Term Memories in Oscillatory Subcycles, *Science* 80- 267:1512-15. doi: 10.1126/science.7878473.
- Lois, C., and Alvarez-Buylla, A. (1994). Long-distance neuronal migration in the adult mammalian brain. *Science* 264, 1145–1148. doi: 10.1126/science.8178174
- López-Bendito, G. (2018) Development of the Thalamocortical Interactions: Past, Present and Future. *Neuroscience* 385, 67–74. doi:10.1016/j.neuroscience.2018.06.020
- Llorens-Martin, M., Trejo, J.L. (2011) Multiple birthdating analyses in adult neurogenesis a line-up of the usual suspects, *Frontiers in Neuroscience* 5(76). doi: 10.3389/fnins.2011.00076
- Liu, K., Ma, W., Li, C. et al (2020) Advances in transcriptional factors related to neuroglial cell reprogramming, *Translational Neuroscience* 11, 17-27, doi : 10.1515/tnsci.2020-0004
- López-Virgen V., Zárate-López, D., Adirsch F.L., Collas-Aguilar, J. (2015) Effects of sleep deprivation in hippocampal neurogenesis, *Gac Med Mex* 151:90-5. PMID: 25739489

- Magó, A., Kis, N., Lükő, B., Makara J.K. (2021) Distinct dendritic Ca²⁺ spike forms produce opposing input-output transformations in rat CA3 pyramidal cells, *eLife* 10:e74493, doi: [10.7554/eLife.74493](https://doi.org/10.7554/eLife.74493)
- Maingret, N., Girardeau, G., Todorova, R., Goutierre, M., Zugaro, M. (2016) Hippocampo-cortical coupling mediates memory consolidation during sleep. *Nat Neurosci.* 19:959–64, doi: 10.1038/nn.4304
- Majewska, A.K., & Sur, M. (2006) Plasticity and specificity of cortical processing networks. *Trends in neurosciences*, 29(6), 323–329. <https://doi.org/10.1016/j.tins.2006.04.002>
- Marin, O., Valiente, M., Ge, X., and Tsai L-H. (2010) Guiding Neuronal Cell Migration, *Cold Spring Harb Perspect Biol* 2(a001834). doi:10.1101/ch.sperspect.a001834
- Martin, J-C. (1994) A connectionist model using multiplexed oscillations and synchrony to enable dynamic connections. In: Marinaro, M., Morasso, P.G. (eds) ICANN 1994. Springer, London, doi: [10.1007/978-1-4471-2097-1_178](https://doi.org/10.1007/978-1-4471-2097-1_178)
- Markram, H., Lübke, J., Frotscher, M., and Sakmann, B. (1997). Regulation of synaptic efficacy by coincidence of postsynaptic Aps and EPSPs. *Science* 275(5297):213-5. doi: 10.1126/science.275.5297.213.
- Marrosu, F., Portas, C., Mascia, M.S. et al (1994) Microdialysis measurements of cortical and hippocampal acetylcholine release during sleep-wake cycle in freely moving cats, *Brain Research* 6, 375-381, doi: 10.1016/j.brainresbull.2006.01.009
- McCloskey, M., & Cohen, N.J. (1989). Catastrophic interference in connectionist networks: The sequential learning problem. In *Psychology of learning and motivation* 24:09-165). Academic Press. doi:[10.1016/S0079-7421\(08\)60536-8](https://doi.org/10.1016/S0079-7421(08)60536-8)
- Medvedeva, V.P., Pierani, A. (2020). How Do Electrical Fields Coordinate Neuronal Migration and Maturation in the Developing Cortex?, *Front. Cell Dev. Biol.* 8:580657. doi: 10.3389/fcell.2020.580657
- Minlebaev, M., Colonnese, M. et al. (2011) Early Gamma oscillations synchronize developing thalamus and cortex. *Science* 334, 226-229. doi: 10.1126/science.1210574
- Mondadori, C., Weiskrantz, L., Buerki, H. et al. (1989) NMDA receptor antagonists can enhance or impair learning performance in animals. *Exp Brain Res* 75:449–456 <https://doi.org/10.1007/BF00249896>
- Monti, J.M. (2011) Serotonin control of sleep-wake behavior, *Sleep Medicine Reviews* 15:269-281, doi: 10.1016/j.smrv.2010.11.003
- Monti, J.M., Jantos, H. (2008) The roles of dopamine and serotonin, and of their receptors, in regulating sleep and waking. *Prog Brain Res* 172:625–46. doi: 10.1016/S0079-6123(08)00929-1
- Morshead, C.M., Reynolds, B.A., Craig, C.G., McBurney, M.W., Staines, W.A., Morassutti, D., Weiss, S., and van der Kooy, D. (1994) Neural Stem Cells in the Adult Mammalian Forebrain: A Relatively Quiescent Subpopulation of Subependymal Cells, *Neuron* 13:1071-82. doi: 10.1016/0896-6273(94)90046-9
- Mountcastle, V.B. (1957) Modality and topographic properties of single neurons of cat's somatic sensory cortex, *Journal of Neurophysiology* 20(4): 408–34. doi:10.1152/jn.1957.20.4.408.

- Mountcastle, V.B. (1997) The columnar organization of the neocortex. *Brain: a journal of neurology*, 120(4): 701–722. doi:10.1093/brain/120.4.701
- Nakajima, M., and Halassa, M.M. (2017) Thalamic control of functional cortical connectivity. *Current opinion in neurobiology* 44:127–131. doi: [10.1016/j.conb.2017.04.001](https://doi.org/10.1016/j.conb.2017.04.001)
- Newcomer, J.W., Farber, N.B. and Olney, J.W. (2000) NMDA receptor function, memory, and brain aging, *Dialogues in Clinical Neuroscience*, 2(3):219-232, doi: 10.31887/DCNS.2000.2.3/jnewcomer
- Ngo, H. V., Fell, J., & Staresina, B. (2020). Sleep spindles mediate hippocampal-neocortical coupling during long-duration ripples. *elife*, 9. doi: 10.7554/eLife.57011
- Nicol, X., Hong, K. P., and Spitzer, N. C. (2011) Spatial and temporal second messenger codes for growth cone turning, *Proceedings of the National Academy of Sciences of the United States of America*, 108(33):13776–13781. Doi: 10.1073/pnas.1100247108
- Nitzan, N., McKenzie, S., Beed, P., English, D.F, Oldani, S, Tukker, J.J., Buzsáki, G., and Schmitz, D. (2020) Propagation of hippocampal ripples to the neocortex by way of a subiculum-retrosplenial pathway, *Nature Communication* 11:1947. doi: 10.1038/s41467-020-15787-8
- Nogueira, A. B., Nogueira, A. B., Veiga, J. C. E., & Teixeira, M. J. (2018) Letter: Human Hippocampal Neurogenesis Drops Sharply in Children to Undetectable Levels in Adults. *Neurosurgery* 83(3), E133–E137. doi: 10.1093/neuros/nyy252
- Nottebohm, F. (1989) bird song to neurogenesis, *Sci Am* 260(2):74-9, doi: 10.1038/scientificamerican0289-74.
- Núñez, A., and Buño, W. (2021) The Theta Rhythm of the Hippocampus: From Neuronal and Circuit Mechanisms to Behavior, *Front. Cell. Neurosc.* 15:649262. doi: 10.3389/fncl.2021.649262.
- Ohira, K. (2018) Regulation of Adult Neurogenesis in the Cerebral Cortex, *J Neurol Neuromed* 3(4):59-64. doi: 10.29245/2572.942X/2018/4.1192
- O’Keefe J, Dostrovsky J. (1971) The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Res.* 34, 171–175 doi: 10.1016/0006-8993(71)90358-1
- Pérez-Rodríguez, D.R., Blanquo-Luquin, I., and Mendioroz, M. (2021) The Participation of Microglia in Neurogenesis: A Review, *Brain Sci.* 11(658). doi:10.3390/brainsci11050658
- Peyrache, A., Khamassi, M., Benchenane, K., Wiener, S., Battaglia, F. (2009) Replay of rule-learning related neural patterns in the prefrontal cortex during sleep, *Nature Neuroscience* 12(7) :919-926. doi: 10.1038/nn.2337
- Piatti, V.C., Ewell, L.A., and Leutgeb, J.K. (2013) Neurogenesis in the dentate gyrus: carrying the message or dictating the tone, *Frontiers in Neuroscience* 7(50):1-11, doi: 10.3389/fnins.2013.00050
- Preston AR, Eichenbaum H. Interplay of hippocampus and prefrontal cortex in memory (2013) *Curr Biol.* 2013 Sep 9;23(17):R764-73. doi: 10.1016/j.cub.2013.05.041
- Puentes-Mestril C. and Aton, S.J. (2017) Linking Network Activity to Synaptic Plasticity during Sleep: Hypotheses and Recent Data, *Front. Neural Circuits* 11:61. doi: 10.3389/fncir.2017.00061

- Rasch, B., Born, J. (2013) About Sleep's Role in Memory, *Physiol Rev.* 93(2):681-766. doi: 10.1152/physrev.00032.2012
- Rasmussen, R., O'Donnell, J., Ding, F., Nedergaard, M. (2020) Interstitial ions: A key regulator of state-dependent neural activity., *Prog Neurobiol* 193(101802), doi: 10.1016/j.pneurobio.2020.101802
- Rauchs, G., Desgranges, B., Foret, J., Eustache, F. (2005) The relationships between memory systems and sleep stages. *J Sleep Res.*14:123–40. doi: [10.1111/j.1365-2869.2005.00450.x](https://doi.org/10.1111/j.1365-2869.2005.00450.x)
- Rothschild, G., Eban, E., and Frank, L.M. (2017) A cortical-hippocampal loop of information processing during memory consolidation, *Nat Neurosci.* 20(2):251-59. doi: 10.1038/nn.4457
- Roumis, D.K., Frank, L.M. (2015) Hippocampal sharp-wave ripples in waking and sleeping states, *Curr Opin Neurobiol* 35:6-12. doi:10.1016/j.conb.2015.05.001
- Schmidt-Hieber, C., Jonas, P., and Bishofberger, J. (2004). Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. *Nature* 429, 184-187. doi: 10.1038/nature02553
- Schreiner, T., Petzka, M., Staudigl, T., and Staresina, B.P. (2021) Endogenous memory reactivation during sleep in humans is clocked by slow oscillation-spindle complexes, *Nature Communications* 12:3112. doi:10.1038/s41467-021-23520-2
- Sherman, S. M. (2017) Functioning of Circuits Connecting Thalamus and Cortex. *Comprehensive Physiology*, 7(2):713–739. doi:10.1002/cphy.c160032
- Shouze, M.N., Staba, R.G., Saquib, S.F., Farber, P.R. (2000) Monoamines and sleep: microdialysis findings in pons and amygdala. *Brain Res.* 860:181–9. doi: 10.1016/s0006-8993(00)02013-8
- Silva, D., Feng, T. & Foster, D. (2015) Trajectory events across hippocampal place cells require previous experience. *Nat Neurosci* 18, 1772–1779, doi: 10.1038/nn.4151
- Singh, N., Lorbeck, M.T., Zervos, A., Zimmerman, J., Elefant, F. (2010) The histone acetyltransferase Elp3 plays in active role in the control of synaptic bouton expansion and sleep in drosophila. *J Neurochem.* 2010;115:493–504. doi: [10.1111/j.1471-4159.2010.06892.x](https://doi.org/10.1111/j.1471-4159.2010.06892.x)
- Sirota, A., Csicsvari, J., Buhl, D., Buzsáki, G. (2003) Communication between neocortex and hippocampus during sleep in rodents, *Proc Natl Acad Sci USA* 100(4):2065-9. doi: 10.1073/pnas.0437938100
- Skelin, I., Zhang, H., Zheng, J., Ma, S., Mander, B.A., Kim McManus, O., Vadera, S., Knight, R.T., McNaughton, B.L., & Lin, J.J. (2021) Coupling between slow waves and sharp-wave ripples engages distributed neural activity during sleep in humans. *PNAS* 118(21), e2012075118, doi: 10.1073/pnas.2012075118
- Slapas, A. G., and Wilson, M. A. (1998) Coordinated Interactions between Hippocampal Ripples and Cortical Spindles during Slow-Wave Sleep, *Neuron* 21: 1123-1128, doi: 10.1016/s0896-6273(00)80629-7.
- Sorrells, S., Paredes, M., Cebrian-Silla, A. *et al.* (2018) Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. *Nature* 555, 377–381. doi: 10.1038/nature25975
- Stoeckli, E.T. (2018) Understanding axon guidance: are we nearly there yet?, *The Company of Biologist Ltd | Development* 145(dev141415), doi: 10.1242/dev.151415

- Sullivan, D. Csicsvari, J., Mizuseki, K., Montgomery, S., Diba, K., and Buzsáki, G. (2011) Relationships between Hippocampal Sharp Waves, Ripples, and Fast Gamma Oscillations: Influence of Dentate and Entorhinal Cortical Activity, *The Journal of Neuroscience* 31(23):8605-8616. doi: 10.1523/JNEURISCI.0294-112011
- Sur, M., & Leamey, C.A. (2001). Development and plasticity of cortical areas and networks. *Nature reviews. Neuroscience*, 2(4), 251–262, doi: 10.1038/35067562
- Sutherland, D.J., Pujic, Z., Goodhill, G.J. (2014) Calcium signaling in axon guidance, *Trends in Neurosciences* 37(8):424-432, doi: 10.1016/j.tins.2014.05.008.
- Szuperak, M., Churgin, M.A., Borja, A.J., Raizen, D.M., Fang-Yen, C., Kayser, M.S. (2018) A sleep state in *Drosophila* larvae required for neural stem cell proliferation, *eLife* 7:e33220. doi: 10.7554/eLife.33220
- Tadros, T., Krishnan, G.P., Ramyaa, R. *et al.* (2022) Sleep-like unsupervised replay reduces catastrophic forgetting in artificial neural networks, *Nat Commun* 13(7742), doi: 10.1038/s41467-022-34938-7
- Tang, L., Pruitt, P.J., Yu, Q, Homayouni, R, Daugherty, A.M., Damoiseaux, J.S., and Ofen, N. (2020) Differential Functional Connectivity in Anterior and Posterior Hippocampus Supporting the Development of Memory Formation, *Front. Hum. Neurosci.* 14, doi: 10.3389/fnhum.2020.00204
- Taxidis, J., Anastassiou, C.A., Diba, K., Koch, C. (2015) Local Field Potentials Encode Place Cell Ensemble Activation during Hippocampal Sharp Wave Ripples, *Neuron* 87:590-604, doi: 10.1016/j.neuron.2015.07.014
- Toffano-Nioche, C., Béroule, D., Tassin, J.-P. (1998) “A Functional Model of some Parkinson's Disease Symptoms using a Guided Propagation Network”, *Artificial Intelligence in Medicine* 14:237-258. doi:10.1016/s0933-3657(98)00036-0
- Tonegawa, S., Liu, X., Ramirez, S., and Redondo, R. (2015) Memory Engram Cells Have Come of Age, *Neuron* 87:918-931, doi: 10.1016/j.neuron.2015.08.002
- Tononi, G., and Cirelli, C. (2014) Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron* 81(1):12–34. <https://doi.org/10.1016/j.neuron.2013.12.025>
- Toth, A. B., Shum, A. K., and Prakriya, M. (2016). Regulation of neurogenesis by calcium signaling, *Cell Calcium* 59(2-3):124-134. Doi: 10.1016/j.ceca.2016.02.011
- Urbain, N., Fourcaud-Trocmé, N., Laheux, S., Salin, P. A., & Gentet, L. J. (2019) Brain-State-Dependent Modulation of Neuronal Firing and Membrane Potential Dynamics in the Somatosensory Thalamus during Natural Sleep. *Cell reports* 26(6), 1443–1457.e5, doi: 10.1016/j.celrep.2019.01.038
- Van Rullen, R., Guyonneau, R., and Thorpe, S.J. (2005) Spike times make sense, *Trends Neurosci.* 28, 1-4. doi: [10.1016/j.tins.2004.10.010](https://doi.org/10.1016/j.tins.2004.10.010)
- Vasković, J. (2023) Cytoarchitecture of cerebral cortex, www.kenhub.com/en/library/anatomy/cortical-cytoarchitecture

- Von der Malsburg, C. (1981) The Correlation Theory of Brain Function, doi: 10.1007/978-1-4612-4320-5_2
- Von der Malsburg, C. (1999). The what and why of binding: the modeler's perspective. *Neuron* 24(1):95-104, 111-25. doi: 10.1016/s0896-6273(00)80825-9.
- Singer, W. (1999). Neuronal synchrony: a versatile code for the definition of relations? *Neuron* 24, 49–65. doi: 10.1016/s0896-6273(00)80821-1
- Wang, X., Liu, H., Morstein, J., Novak, A.J.E., Trauner, D., Xiong, Q., Yu, Y., and Ge, S. (2020) Metabolic tuning of inhibition regulates hippocampal neurogenesis in the adult brain, *PNAS* 117(41), 25818-29. doi: 10.1073/pnas.2006138117
- Watson, J.C., Baghdoyan, H.A., and Lydic, R. (2010) Neuropharmacology of Sleep and Wakefulness, *Sleep Med Clin.* 5(4): 513528. doi: 10.1016/j.jsmc.2010.08.003
- Wenger, E., Kühn, S., Verrel, J., Mårtensson, J., Bodammer, N.C., Lindenberger, U., Lövdén, M. (2017) Repeated Structural Imaging Reveals Nonlinear Progression of Experience-Dependent Volume Changes in Human Motor Cortex, *Cerebral Cortex*, Volume 27(5):2911–2925, doi: 10.1093/cercor/bhw141
- Westerlund, P., Bérouté, D., Roques, M. (1996) “Experiments in Robust Parsing with a Guided Propagation Network”, *New Methods in Language Processing*, D.Jones (Ed.), UCL Press, London. ISBN: 0001857287118
- Whitehurst, L.N., Cellini, N., McDevitt, E.A., Duggan, K.A., and Mednick, S.C. (2016) Anatomic activity during sleep predicts memory consolidation in humans, *PNAS* 113(26). doi:10.1073/pnas.1518202113
- Yang, G., Wan Lai, C.S., Cichon, J., MA, L., Li, W., and Gan, W-B. (2015) Sleep promotes branch specific formation of dendritic spines after learning, *Science* 344(6188): 1173-78. doi:10.1126/science.1249098
- Yonelinas, A., Ranganath, C., Ekstrom, A., Wiltgen, B. (2019) A contextual binding theory of episodic memory: Systems consolidation reconsidered, *Nat Rev Neurosci.* 20(6):364-375. doi:10.1038/s41583-019-0150-4
- Željka, K., Visnja, M., Lana, V., Hao, H., Ivica, K. (2017) Growth of Thalamocortical Fibers to the Somatosensory Cortex in the Human Fetal Brain, *Frontiers in Neuroscience* 11, doi: 10.3389/fnins.2017.00233
- Zhang, H., and Jacobs, J. (2015) Travelling Theta Waves in the Human Hippocampus, *The Journal of Neuroscience* 35(36):12477-12487, doi: 10.1523/JNEUROSCI.5102-14.2015
- Zhang, X.M., Cai, Y., Chu, Y., Chen, E.Y., Feng, J.C., Luo, X.G., Xiong, K., Struble, R.G., Clough, R.W., Patrylo, P.R., Kordower, J.H., Yan, X.X. (2009) Doublecortin-expressing cells persist in the associate cerebral cortex and amygdala in aged nonhuman primates. *Frontiers in Neuroanatomy* 3:17. doi:[10.3389/neuro.05.017.2009](https://doi.org/10.3389/neuro.05.017.2009)

Programming a GP system with pulse signals

2 Guided Propagation (GP) data structures and algorithm

1.1 Data structures

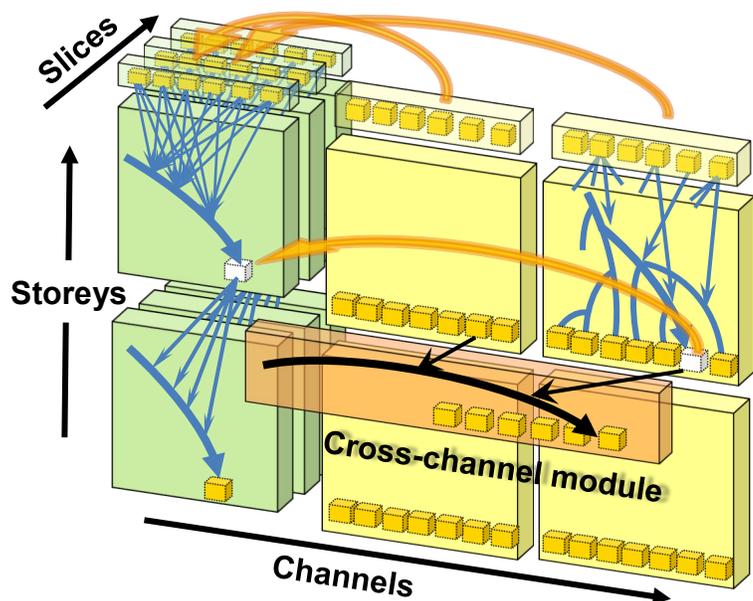
Whereas a pre-wired network can be represented by a fixed-size array of connections, a dynamic memory of the GP type must link as many network nodes as requested by its learning algorithm in the course of processing. Regardless of the physical placement in the computer memory of two such nodes (e.g.: ‘known *A*’ and ‘new *B*’), *A* can be associated with a pointer that indicates the address dynamically assigned to *B* through learning. If *A* must later on be connected to other new elements, the former should be associated with a list of pointers instead, named “linked list” in *object-oriented programming*.

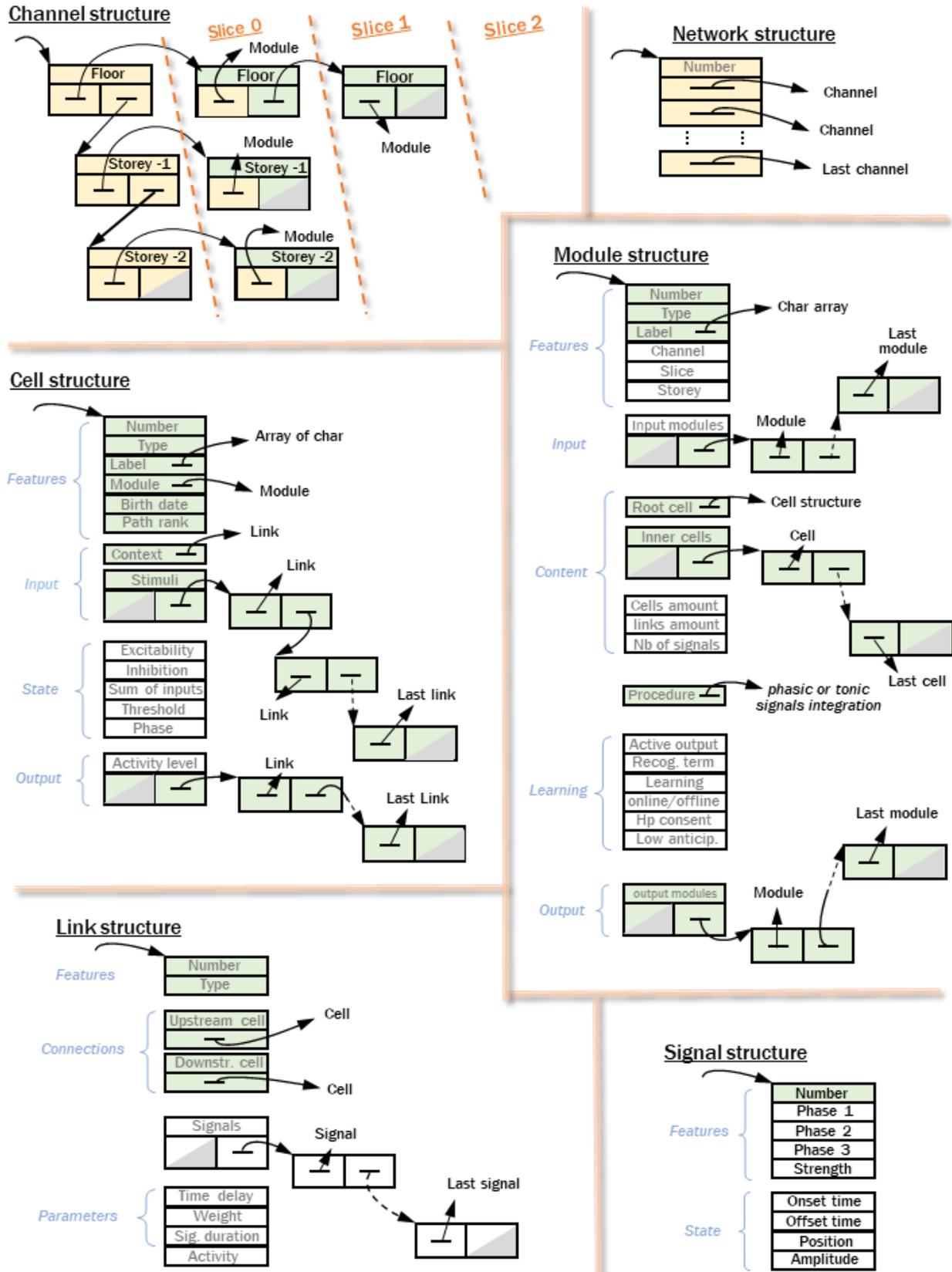
A basic GP node (i.e.: “elementary processing unit”, or simply “cell”) is therefore represented by linked lists of its expandable input/output connections, plus arrays of information about its fixed features, variable parameters and current state of activity. Embedded structures are organized accordingly: signals on links at the input/output of cells hosted by modules that intersect channels and storeys (Sup. Figs. 1 and 2). Given the main part played by the low-level handling of pointers, the first GP simulation had been written in the *ASM86 assembly language* (B roule, 1985), before higher-level programming in *C language* (Weiss, 1985) could provide a more tractable tool, gradually updated over years.

1.2 Management of parallel processing

Inherently parallel, a GP system operation can be sliced into a series of time-frames paced by an internal clock. Across each time-frame, the set of active processing units is scanned so as to move their input signals one step further, and create new output signals for units whose decision threshold has just been crossed. Longer cycles coexist, including for detecting stimuli that did not contribute to GP during the last frames, a criterion that may induce the network expansion. Phasic signalling with embedded cycles, as simulated in this article, requires more advanced processing. One pulse signal has an onset and an offset time at a characteristic position (i.e.: phase) within a fixed interval of several frames. A compound pattern identified by a series of phases forms a longer interval within the replay cycle. Several sequences of compound patterns can thus be replayed (Sup. Fig. 3).

Supplementary Figure 1. Instance of GP architecture that unfolds in three dimensions. The channel in green (*Hp* in this article) contains two preset storeys, while its slices develop dynamically in order to accommodate new short-term memories (STM). The pattern detector/ generators (PDGs) at the bottom of every channel in yellow (*Cx*) are linked to *Hp* (orange arrows) as well as cross circuits (in orange) that allow modulation (e.g.: anticipation) to be conveyed between modules.





Supplementary Figure 2. Data structures of a GP network. Instances of these embedded types (i.e.: network, channel, module, cell, link, signal) are manipulated through object-oriented programming: a combination of dynamic list structures and arrays of values, either ongoing variables (white background) or fixed, either at startup (yellow background) or at their creation by learning (green background).

1.3 Management of embedded pulse signals

Let *PhasesCycle* be the period (T_1) wherein the current phase of a GP module is incremented within the $[1, NbPhases]$ range as the internal clock proceeds. *NbPhases* is also the maximum number of patterns that can be simultaneously retained without interference. In order to store at most *NbPatterns* of such patterns, *PhaseCycle* is embedded into a longer cycle T_2 : $CombPhasesCycle = NbPatterns \times T_1$.

CombPhasesCycle is itself embedded into the largest time interval T_3 during which a sequence of patterns can be replayed: $ReplayCycle = NbComplexPatterns \times T_2$.

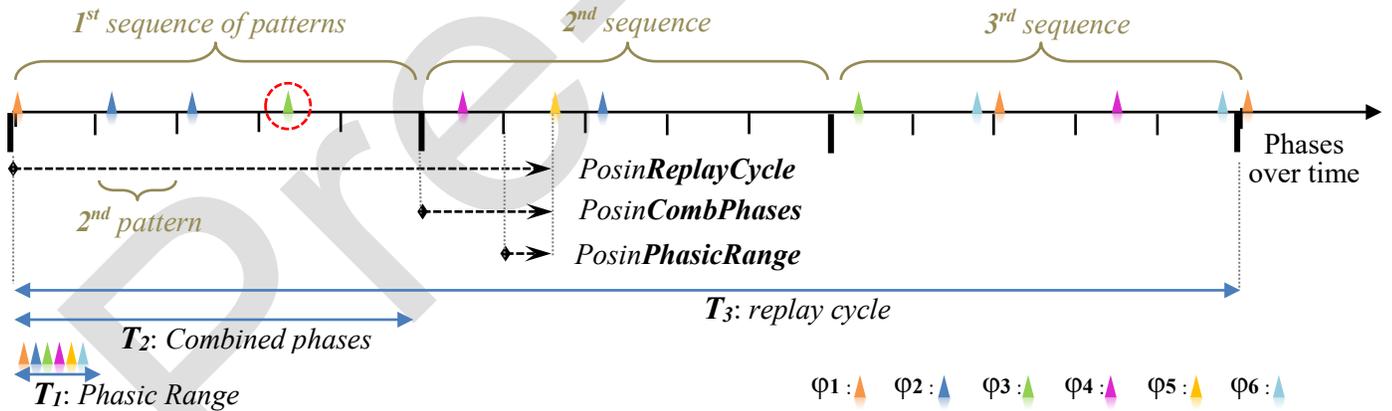
Let “*Posin*” stand for “position in”, and “*time*” be the ongoing value of the system inner clock. The current time-position within the current *ReplayCycle* is given by $PosinReplayCycle = time \% ReplayCycle$, where % (i.e.: modulo) gives the remainder of *time* divided by *ReplayCycle*. Then, the time elapsed from the beginning of the current T_2 that contains several patterns is given by: $PosinCombPhases = PosinReplayCycle \% CombPhases$. Finally, position in T_1 , namely the current phase, is: $PosinPhasicRange = PosinCombPhases \% PhasesCycle$.

The current replay cycle is: $ReplayCycle_Num = time / ReplayCycle + 1$

Current sequence of patterns: $CombPhases_Num = PosinReplayCycle / CombPhases + 1$

Current pattern: $PhasicRange_Num = PosinCombPhases / PhasicRange + 1$

A pulse signal is mostly defined by its characteristic *Phase 1*, namely the pattern it codes for, the rank of this pattern in a sequence (*Phase 2*), and the rank of the sequence in a replay cycle (*Phase 3*).



Supplementary Figure 3. Embedded time-frames T_1 , T_2 , T_3 , that respectively host embedded patterns to be replayed. In the example displayed here, 6 distinct phases and therefore 6 possible patterns can be combined in sequences of 5 patterns at most. Three such sequences form here a replay cycle T_3 . A given signal owns 3 phases: *Phase 1* shared with its associated pattern, *Phase 2* that corresponds to the rank of its pattern in a sequence, and *Phase 3* that gives the rank of its sequence within a replay cycle. For the pulse signal circled in red: *Phase 1* = 3 (ϕ_3), *Phase 2* = 4, and *Phase 3* = 1.

Hippo-Cortical sleep-wake cooperation

1.4 Digest of the GP algorithm with embedded pulse signals

Main Program

```

{   time = 1
  For every time frame:
    For every Channel:
      For every Module:
        Learning( Module ) *
        For every Cell:
          For every input Link:
            {
              For every conveyed Signal:
                {
                  Increment the signal position
                  if ( Signal position >= Signal beginning ) /* delayed integration */
                    then
                      {
                        if ( Signal Phase 1 = current Module phase
                          and (( Signal Phase 2 = PhasicRange_Num ) or Phase 2 = 0 )
                          and (( Signal Phase 3 = CombPhases_Num ) or Phase 3 = 0 ) )
                          then Signal onset; increase the sum of signals.
                        if ( Signal position = signal end )
                          then Signal offset. Decrease the sum of signals.
                      }
                }
              if ( Sum of input signals > cell threshold ) /* Summation of cell inputs */
                then For every output link: create a signal /* New output signal */
            }
          Increment time
        }

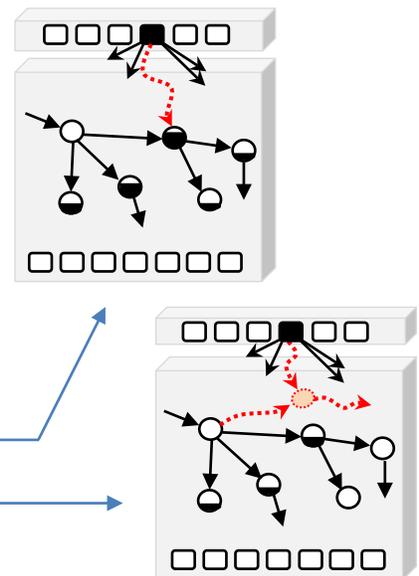
```

*Learning(Module)

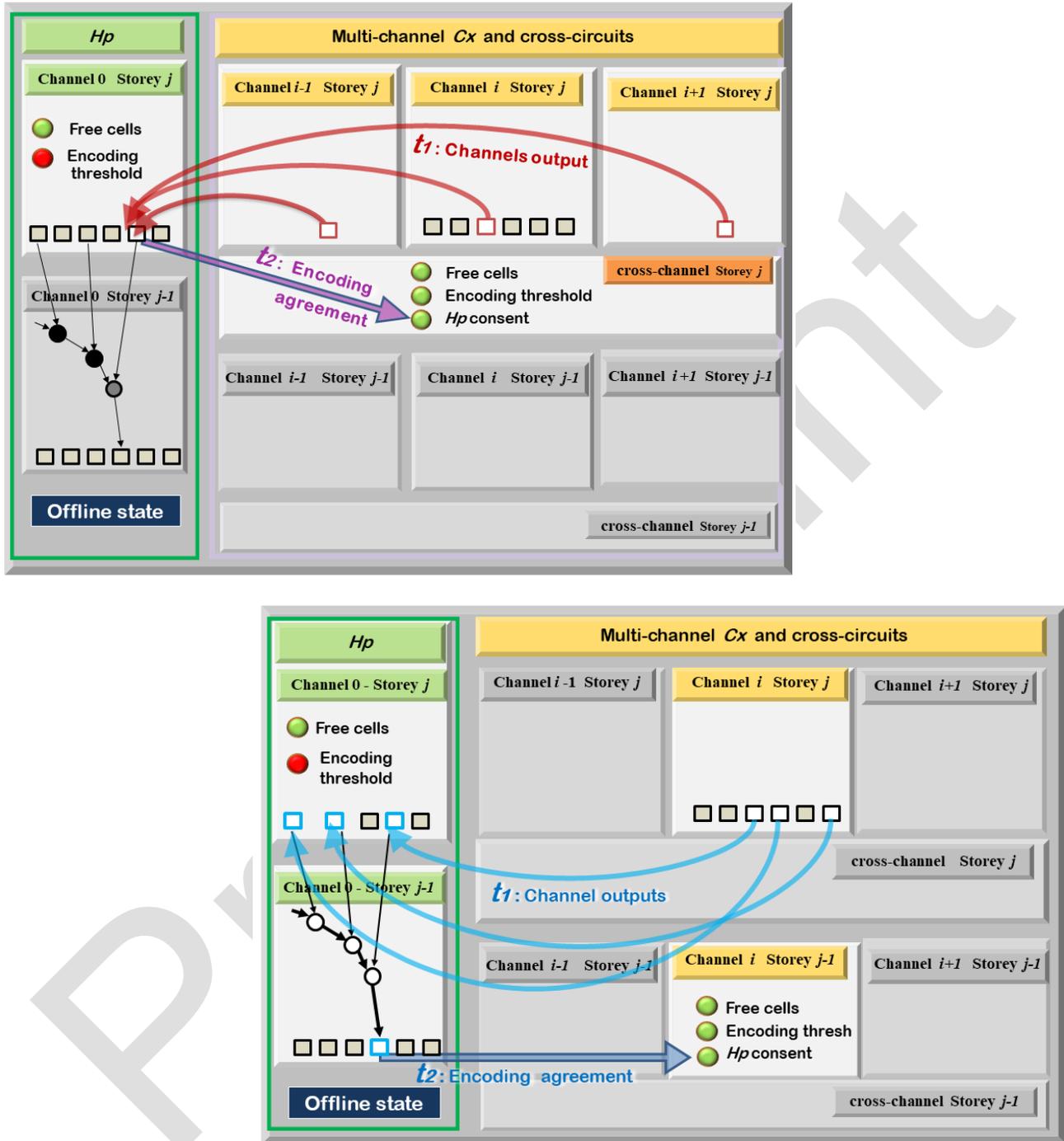
```

{
  if ( Active_output( Module )
    then for every module below:
      Reco deadline ( Module ) = Module period
  if ( deadline reached )
    then facilitation of all stimuli ( Module );
  Delay( Module ) = 3
  Decrement: Reco deadline ( Module )
  Decrement Delay ( Module )
  if ( Delay( Module ) = 1 )
    then for every stimulus( Module ): /* module above */
      if ( activity( stimulus ) > ActMin )
        then seeking the most active coincident CD-unit
          if ( CD-unit found )
            then if ( signal inputs > threshold( CD-unit ) )
              Generalization( CD-unit )
            else
              Differentiation ( CD-unit )

```

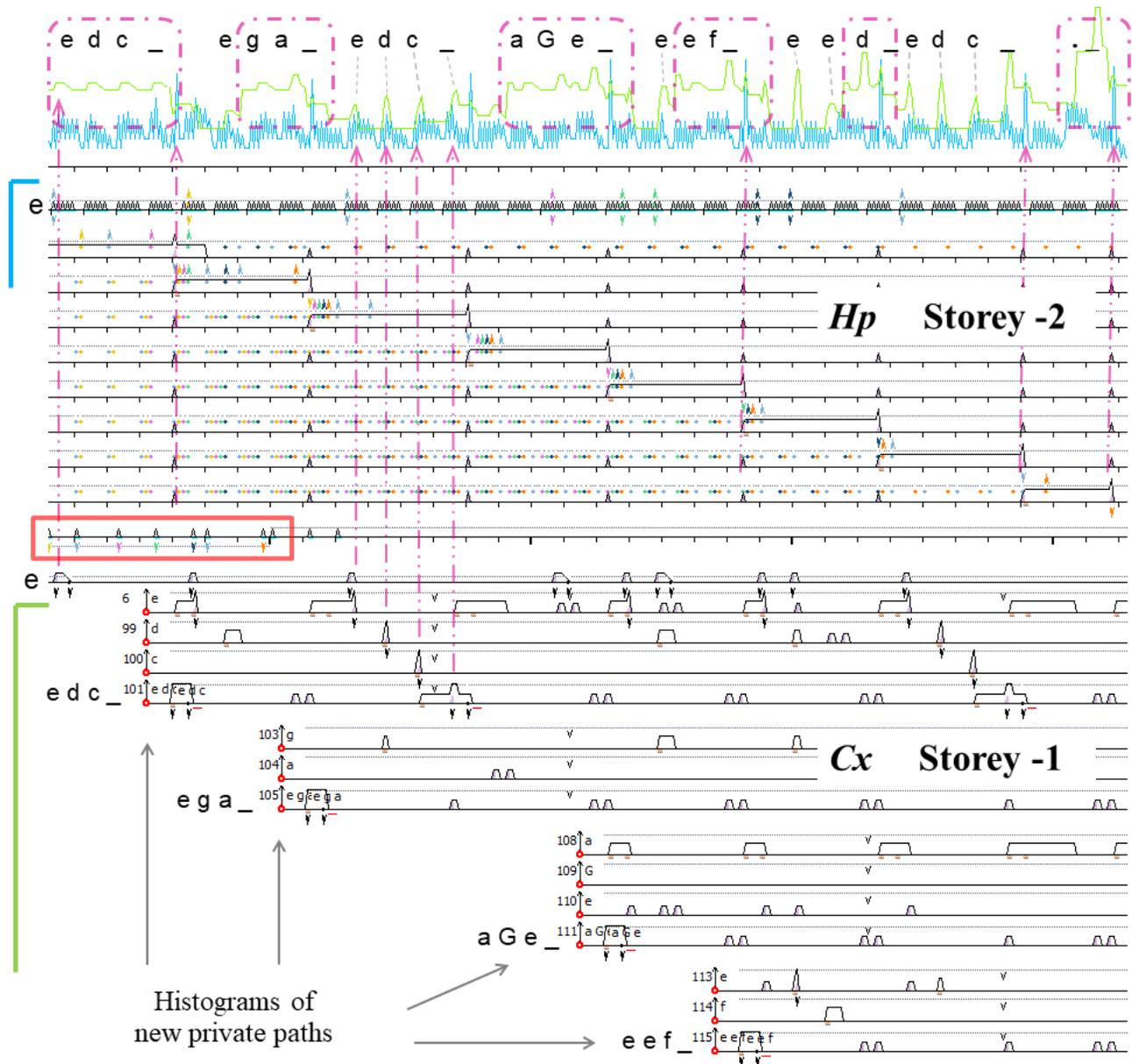


3 Offline development of a GP system with several Cx channels

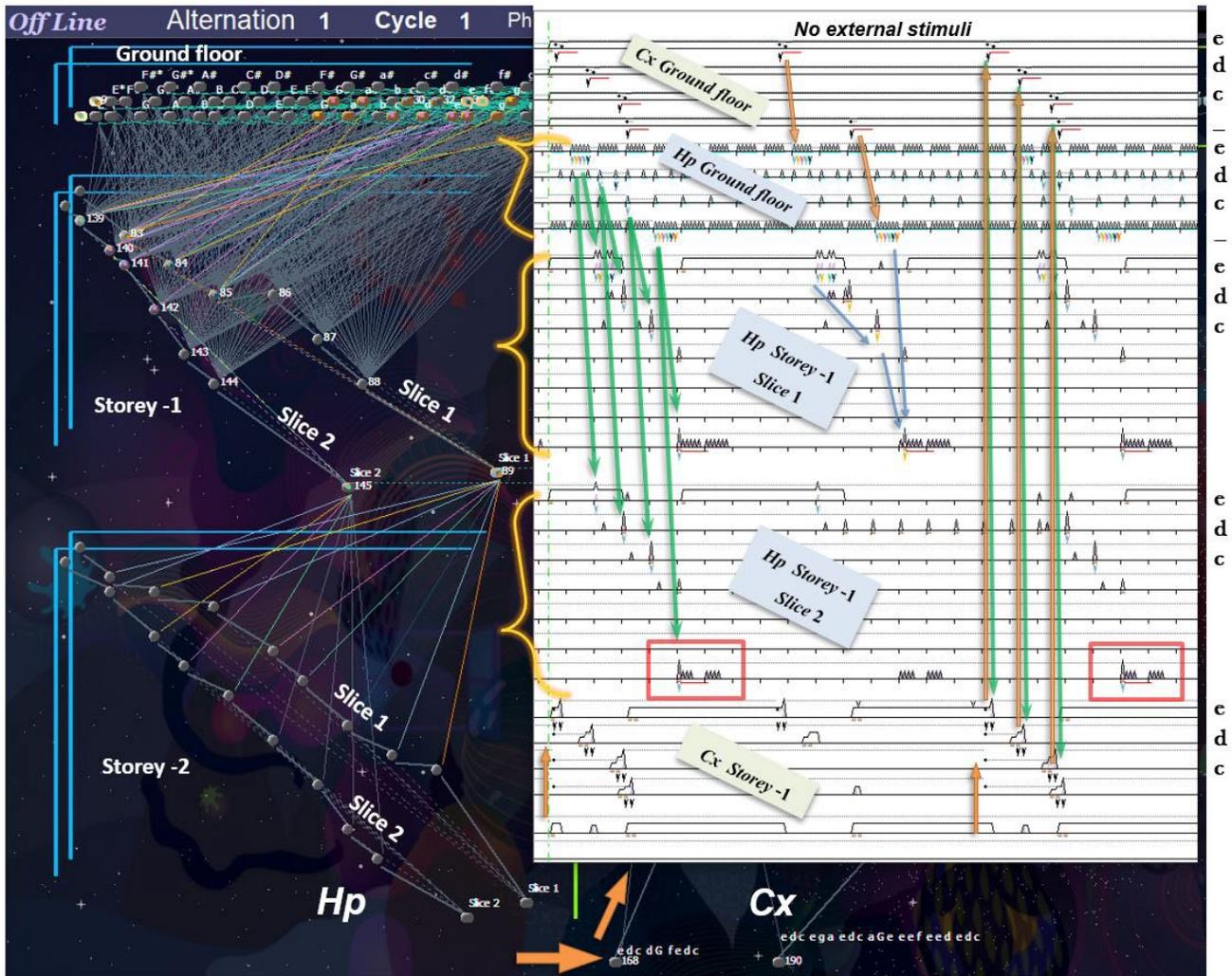


Supplementary Figure 4. Visual representation of the control of paths creation in parallel Cx channels (algorithm used in: Béroutte, 2018). The extension of a Cx module is conditioned by the availability of free cells, anticipation decrease and stoppage (when: “Encoding threshold reached”) as well as the agreement of Hp (“Hp consent”): In the top frame, paths that code for the same pattern in different channels must be completed before connecting them to a cross-channel path (in orange). This occurs when one Hp output has received signals from all its Cx partners in different channels (red arrows). In the bottom frame, a compound pattern cannot be built before the completion of all its components of the same channel (blue arrows). In this case, Hp gives its consent when its deeper storey has an active output.

Hippo-Cortical sleep-wake cooperation



Supplementary Figure 5. Mapping of global activities of phasic and tonic GP channels onto local signals during the replay of a trajectory (letters displayed at the top stand for the combination of notes that form the melody of “Let it be” (Beatles, 1970)). The blue curve then shows the cyclic rising of *Hp* high-rate phasic activity tied to the pattern in progress. The green curve above reflects the tonic channel (*Cx*) activity, displaying two kinds of shape depending on the novelty of the ongoing pattern. Would the latter not already be represented in LTM, a wide wave results from the overactivation of a path under construction, whereas more discreet bursts accompany the identification of a known pattern (i.e.: ‘e d c ’). Of note, the global tonic activity consistently tends to increase with the incorporation of add-on units into *Cx*. Owing to the full availability of free units simulated in this computer session, dedicated paths are built across a single tonic replay initiated by a series of *Hp* pulses (bounded here by a red square), as witnessed by the successive appearance of histograms automatically displayed on new paths completion (diagrams at the bottom).



Supplementary Figure 6. Over-activation of the *Hp* channel slices by the tonic replay of a single *Cx* path. In absence of external stimuli, an upward facilitation (thick orange arrow at the bottom) spreads from *Cx* to *Hp* across the ground floor where PDGs get activated. Here, two generic paths convey the same sequence (“e d c _”), possibly at different phases in different slices. Since the square tonic signals span over the entire phase interval, not only a proper response occurs in slice 1, but also irrelevant firing in slice 2 (shown in two red boxes), which is subdued by contextual information in the deeper storey -2 of *Hp* slice 2.

References

- Béroule, D. (1985) Un Modèle de Mémoire Adaptative, Dynamique et Associative pour le Traitement Automatique de la Parole, Thèse de 3^{ème} Cycle, Université de Paris-Sud, Centre d’Orsay.
- Weiss, F. (1985) Etude de l’adaptation des délais de transmission dans un réseau à propagation d’énergie pour la reconnaissance automatique de la parole, Rapport de DEA, Université de Paris-Sud, Centre d’Orsay.
- Béroule, D. G. (2018) Offline encoding impaired by epigenetic regulations of monoamines in the guided propagation model of autism. *BMC neuroscience*, 19(1), 80. <https://doi.org/10.1186/s12868-018-0477-1>