MÉMOIRE POUR L'HABILITATION À DIRIGER DES RECHERCHES (HDR)

FROM INTRINSIC IONIC CONDUCTANCE TO TEMPORAL COMPUTATIONS

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Table of Contents

1. Introduction

I have been working, since my Ph.D. thesis, in the field of computational neurosciences. My main interest has been to understand the dynamical mechanisms underlying plasticity and memory, by conceiving, analyzing and simulating neural models at the molecular, cellular and network levels.

A large part of my scientific activity has been devoted to the study of the possible contribution of intrinsic ionic conductance in shaping firing patterns involved in neural computations that present strong temporal aspects at the behavioral time scale. Hence, I have developed biophysically realistic single neuron models to assess how conductance such as the persistent sodium or the slowly-inactivating potassium conductance can account for the ON (**Part 2)** and OFF (**Part 3**) transitions of persistent firing, a landmark of retrospective working memory [1,2]. Later, I have theoretically assessed how the slowly-inactivating potassium conductance may account for the temporal integration of information in medium spiny neurons of the rat striatum *in vivo* (**Part 4**; collaboration with Pr S. Charpier and Dr S. Mahon; [3,4]) and to the control of ramp-like firing in the cortex, which is commonly thought to sub-serve prospective memory (**Part 5**; [5]). In parallel, I have proposed a theoretical description of how physiological and pathological aspects of neuronal excitability may be understood in terms of temporal properties in the context of dynamical systems [5]. More recently, I have proposed, in collaboration with Dr S. Genet, a realistic model of the complex electrophysiology of the Purkinje cell. In particular, this theoretical study offers a detailed account of plateau potentials and the prediction of valley potentials, (their mirror signals), which have been observed since. Together, these signals provide strong temporal computational abilities to Purkinje cells (**Part 6**; [6,7]).

More recently, I have been studying dynamical properties of the mechanisms and role of plasticity and memory in the nervous system. Specifically, I have developed, with Dr S. Genet, a model of activity-dependent kinase/phosphatase cycles that represents, to our knowledge, the first biophysically realistic account of the opposing dynamical requirements of plasticity and memory, i.e. rapidity versus slowness. Hence, this study thus provides a new principle for plasticity and memory that is based on graded information and the emergence of an activity-dependent time-constant (**Part 7**; [8]). In particular, this study was aimed at providing a biophysically realistic theoretical framework to describe the plastic rules underlying intrinsic plasticity (see next paragraph). In parallel, I have collaborated with Drs H. Berry, and B. Cessac on the effects of Hebbian plasticity on the synaptic structure of

recurrent neural network models [9,10]. This line of studies has shown that the dynamical regime of such networks (fixed point, limit cycle, chaos) can be dictated by biologically realistic synaptic learning rules.

Lately, I have developed a program of several related studies aimed at unraveling the mechanisms and functional roles of intrinsic plasticity (IP), i.e. the activity-dependent plasticity of intrinsic ionic conductance in the central nervous system (**Part 8).** In collaboration with Pr S. Charpier and Dr S. Mahon, we have explored the diversity of IP of rate coding *in vivo*, i.e. activity-dependent modifications of the intensity-frequency relation of neurons. We have found a large repertoire of IP effects, including bidirectional modifications of the threshold or gain, or both [11]. We currently terminate, with J. Naudé, the Ph.D. candidate I supervise, a large theoretical study aimed at unraveling the mechanisms of this diversity, based on the role of biophysical parameters of ionic conductance regulated by IP (*Manuscript in revision in PLoS Comp Biol*). Based on the results obtained *in vivo* (**Part 8**; [11]), the mechanisms of rate coding IP at the cellular level and our knowledge of graded plasticity and memory (**Part 7**; [8]), we currently study the possible functional role of IP at the network level. Specifically, the goal is to study the effect of 1) homeostatic IP on the dynamical regime of activity and pattern sensitivity (with Drs H. Berry and B. Cessac; *Manuscript in preparation*) and 2) anti-homeostatic IP on long-lasting activities in recurrent neural network models.

I develop this last point in a project for the next years in **Part 9**. Current neural network models aimed at accounting for persistent firing patterns, which are thought underlying cardinal cognitive abilities such as decision-making, motor coordination or working memory, leaves important unanswered issues related to their dynamics, statistics and plasticity. These theoretical studies have mostly emphasized the existence of persistent activities as a product of neuronal network operations through recurrent excitatory and inhibitory connections. The present project is aimed at addressing the arguable hypothesis that the dynamical properties provided by intrinsic conductance and intrinsic plasticity of neurons offer plausible biophysically and biochemically answers to these open questions, a possibility that has remained unexplored yet.

2. Intrinsic bistability in neocortical neurons

It was reported *in vitro* that layer V cortical neurons in the neocortex respond to a brief depolarizing pulse by a sustained discharge lasting up to 20 s in the absence of any excitatory synaptic transmission [12]. These results suggest that cortical neurons can be bistable, i.e. they display a stable silent state and a state of stable spiking. Moreover, Silva and colleagues have shown that this rhythmic property of layer V neurons was necessary and sufficient to generate rhythmic patterns at the scale of the network. This behavior is of high interest because it represents an alternative or synergistic mechanism to recurrent connectivity in the generation of selective self-sustained activities, the basic mechanism of short-term memory. [13,14].

The cellular mechanism of this bistability is unknown, although it was demonstrated that it relies on a sodium conductance [12]. Experimental and theoretical evidence suggests that a persistent sodium (NaP) conductance dominates the excitability of pyramidal neocortical neurons at membrane potentials below the action potential threshold [15] and contributes to sub-threshold oscillations and repetitive firing behavior [16]. Therefore, the question arises whether the NaP conductance represents a possible molecular determinant of neocortical neuronal bistability. To do so, I have built and studied in collaboration with Dr. A. Klaassen single and multi-compartimental models of neocortical pyramidal neurons endowed with the leak, sodium and potassium action potential conductance and the NaP conductance [1,2].

As a general rule, we have found in the single compartment model [2] that the discharge mode of the neuron was strongly affected by the maximal conductance of the persistent sodium current, when it was varied in the range of physiological values observed empirically ($0-0.3 mS cm^{-2}$; i.e. 0–1.5% of $\overline{g}_{Na}$ [17]). Indeed, the neuron elicited a single action potential with $\overline{g}_{NaP} = 0 mS cm^{-2}$ (Fig. 1A). Increasing $\overline{g}_{NaP}$, we found that the neuron admitted a stable resting potential, but that transient stimulation induced a stable rhythmic self-regenerative discharge (Fig. 1B). Thus the neuron was bistable. For larger values of $\overline{g}_{NaP}$, the neuron was found to have a spontaneous regenerative (pacemaker) discharge (Fig. 1C).

Moreover, we have shown that 1) bistability is a robust behavior that does not depend upon specific leak conductance values (i.e. membrane passive time constants; Fig. 2A), 2) it arises at low frequencies that are compatible with those observed *in vivo*, even when one considers coarse-grained regulation of its maximal conductance (Fig. 2B), and 3) it relies on substantial NaP activation during the entire inter-spike (ISI) interval, a mechanism that was

robust to the injection of a constant depolarizing current, which mimicked the more depolarized steady-state potential encountered *in vivo* (Fig. 3F). These observations, as well as the robustness of the bistability point to the likely involvement of the persistent sodium conductance in regenerative firing in neocortical cells. However, other conductance such as high-threshold calcium or calcium-activated cationic conductance have been implicated in the maintenance of bistable or multistable cellular firing [18,19,20]. The prediction of our model could be tested experimentally using a specific antagonist of the persistent sodium current [21].

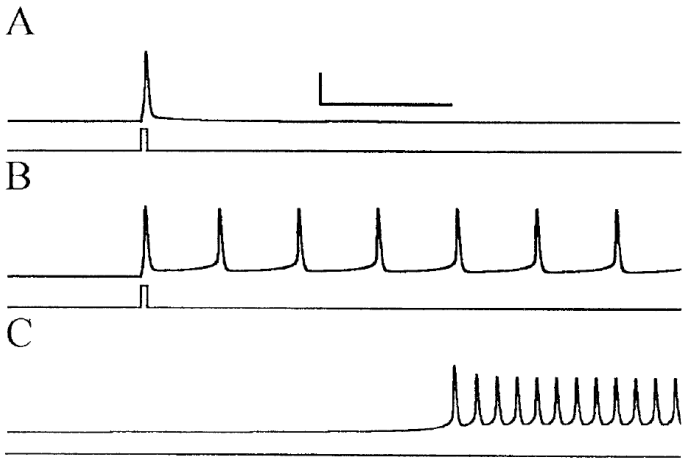

Fig. 1. Firing modes of the model neuron: **A.** transient (T), **B.** bistable (S), **C.** spontaneous sustained (spS). See text. Scale bars (50 ms, 50 mV) apply to all traces (from [2]).

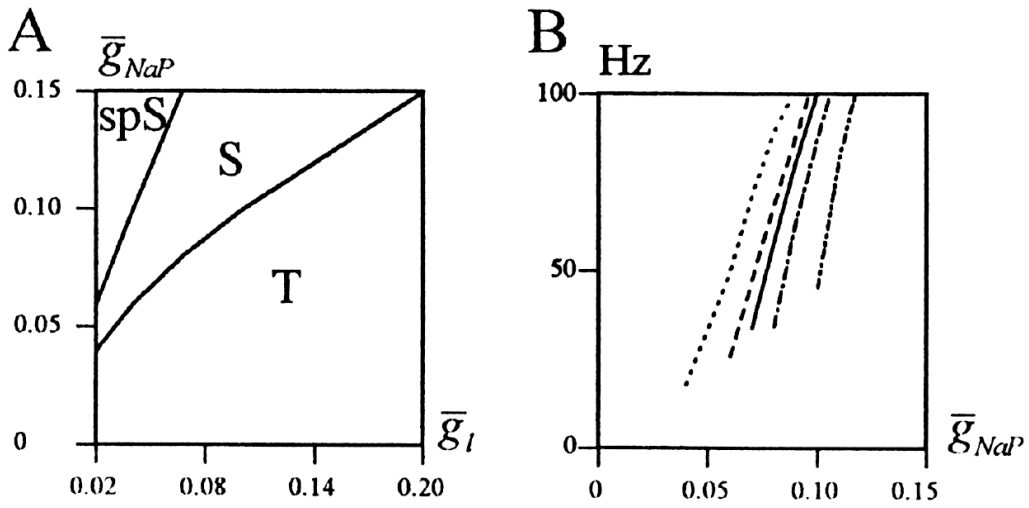

Fig. 2. A. Transient (T), bistable (S) and spontaneous sustained (spS) domains of discharge in the $\left(\overline{g}_{NaP},\overline{g}_L\right)$ plane, where $\overline{g}_L$ denotes for the leak conductance. (B) Firing frequency in the bistable (S) and spontaneous (spS) domains depends on $\overline{g}_{NaP}$ and $\overline{g}_L$ ($0.02 mScm^{-2}$, dotted line; $0.04 mScm^{-2}$, dashed line; $0.05 mScm^{-2}$, solid line; $0.067 mScm^{-2}$, dotted-dash line; $0.1 mScm^{-2}$, double dotted-dash line; adapted from [2])

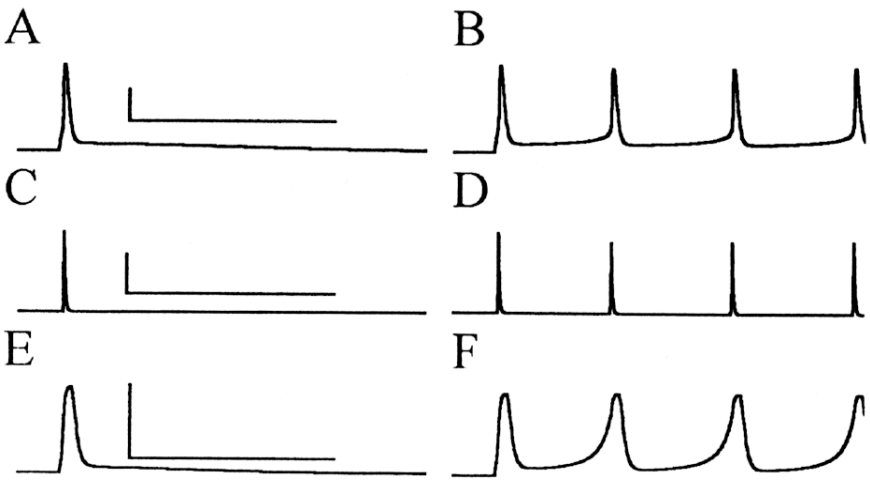

Fig. 3. Membrane potential (**A, B**), fast sodium conductance (**C, D**), and persistent sodium conductance (**E, F**) of the transient (left traces, $\overline{g}_{NaP} = 0.06 mS cm^{-2}$) and sustained discharges (right traces, $\overline{g}_{NaP} = 0.07 mS cm^{-2}$). $\overline{g}_L$ was $0.05 mS cm^{-2}$. Scale bars correspond to 50 ms (all traces), 50 mV (A,B), $5 mS cm^{-2}$ (C,D), and $0.05 mS cm^{-2}$ (E,F). (from [2]).

3. OFF transitions in bistable neocortical neurons

The persistent sodium conductance is commonly balanced in cortical neurons by a slowly-inactivating potassium (Ks) conductance, a conductance known to determine latency to first spike, an important timing properties of neurons [22]. Moreover, both conductance are regulated in frontal cortex neurons by dopamine which is essential to working memory [23].

I have assessed in a pyramidal cortical neuron model the interaction of the NaP and Ks conductance in the generation of bistability [1] and shown that bistability appears as a large domain of the $(\overline{g}_{NaP}, \overline{g}_{Ks})$ plane, so it is robust (Fig. 4). Because dopamine up-regulates $\overline{g}_{NaP}$ and down-regulates $\overline{g}_{Ks}$ [23], this result suggests that it would promote bistability in frontal cortical neurons. Moreover, in the domain of bistability, our model predicted that two successive excitatory synaptic inputs could induce an ON and an OFF transition. During the OFF transition, the increased spike frequency induced by the excitatory input led to an overwhelming cumulative recruitment of Ks conductance; in turn, the slow deactivation (and slower inactivation) of the Ks conductance dampened the voltage back to the resting potential (Fig. 5, stars). This mechanism is potentially very interesting, as it provides a mechanism for OFF transitions of self-sustained activities, which most likely represent an essential computation operation underlying short-term memory in higher cortical areas, while avoiding the requirement for a specific inhibitory connectivity dedicated to the termination of sustained activities.

It has been demonstrated that excitatory synaptic inputs can turn OFF recurrent balanced persistent cortical activity *in vitro* through a phasic increase of the firing frequency in local layer II-VI prefrontal and occipital cortical circuits [24]. Recently, the details of such a recruitment mechanism has been observed empirically *in vitro* in layer III neurons of the lateral entorhinal cortex [25]. These neurons are bistable under muscarinic stimulation and ON transitions involve a calcium conductance while OFF transitions require a calcium-activated potassium conductance recruited by the terminating excitatory synaptic drive. Consistent with this, it was demonstrated in layer V pyramidal prefrontal neurons that too large excitatory inputs (triggering >6 spikes) inhibits the onset of persistent firing due to the recruitment of a slow hyperpolarizing intrinsic current [26]. Thus, recruitment of potassium conductance may represent a general mechanism to terminate sustained activities upon phasic activation by a sensory cue or a copy of the motor response [27]. Alternative mechanisms have been proposed. For instance, a phasic excitatory pulse to the entire neural network can terminate selective persistent activity in a subset of neurons and bring them back to the low-

rate of spontaneous discharge [28]. Another mechanism has been proposed accounting for OFF transitions in spatially structured networks [29] in which persistent activity is ensured by a collective asynchronous discharge whereby a fraction of all neurons is active at every time bin. Triggering a synchronous discharge in the entire network induces a synchronized repolarization of all neurons, disrupting asynchronous collective transmission of the discharge to other neurons, resulting in the OFF transition. The question of whether this transition results from synchronization of synaptic transmission in the network or from the recruitment of intrinsic outward conductance in neurons actually remains an open debate.

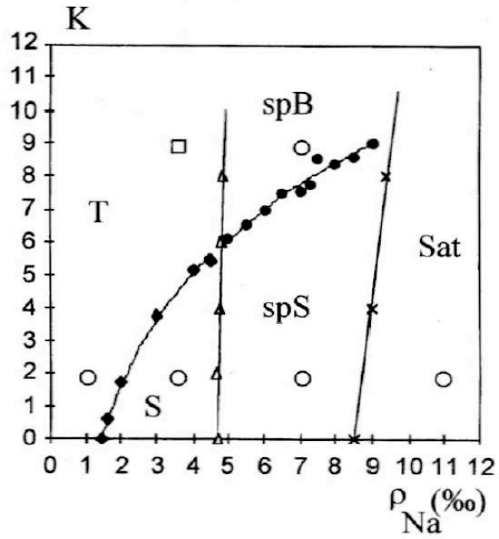

Fig. 4. Transient (T), bistable (S), spontaneous spiking (spS), spontaneous bursting (spB) and saturation (Sat) domains of discharge in the NaP and Ks maximal conductance plane (from [1]).

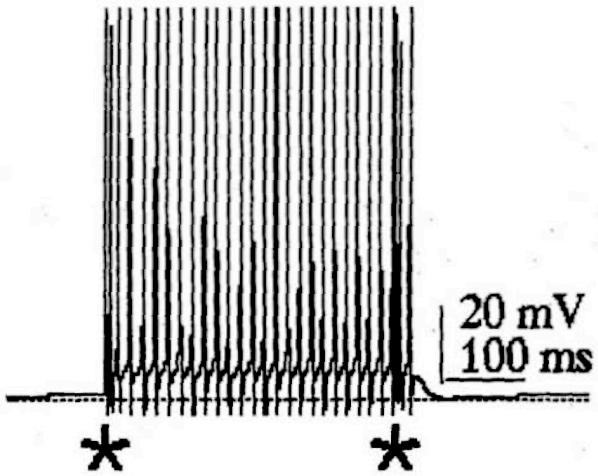

Fig. 5. ON and OFF transitions triggered by two successive inputs (stars) in a bistable neuron endowed with balanced inward an outward conductance (from [1]).

4. Memory of excitation and temporal integration of inputs by slowly-inactivation potassium (Ks) conductance in striatal output neurons (SONs)

In nervous systems, bridging behaviorally relevant events that are temporally separated in time may relies on mechanisms at odds with the explicit short-term memory of past events by self-sustained activity. For instance, the response of GABAergic striatal output neurons (SONs) to incoming excitatory cortical inputs *in vivo* is dependent on the history of past inputs at the time scale of the second [4]. This ability is essential, since the striatum represents the main input stage of the basal ganglia, integrates glutamatergic synaptic inputs from many converging cortical neurons and constitutes a dynamic neural network that is involved in the adaptive control of behavior [30].

SONs display delayed spiking responses to threshold current pulses that have been attributed to a slowly-inactivating potassium current (IKs or IAs; [31]). I have assessed the possible implication of this conductance in the temporal integration of excitatory cortical inputs observed *in vivo* [4] in a model of SONs that included cardinal voltage-gated conductance found in these neurons [3]. Specifically, SONs display an activity-dependent increase in excitability that expresses as a decrease in latency-to-first-spike in response to two successive injected currents (Fig. 6A), as well as through an increase in the probability for spiking in response to threshold cortico-striatal after a direct injection of depolarizing current *in vivo* (Fig. 6B). The latency-to-first-spike reduction displayed a single exponential time-dependence as a function of the inter-stimulus interval (ISI) with time constant $\tau = 0.41s$ (Fig. 6C).

In the model I have built, the As conductance accounted for the activity-dependent increase in excitability observed *in vivo* both in response to direct current injections (Fig. 7A) and synaptic inputs (see [3]). Moreover, the model reproduced its time-dependence (Fig. 7B) and unambiguously demonstrated that the As conductance was both sufficient to the excitability increase (Fig. 7C and 2D). Central to the demonstration, the model shows that the increase in excitability arises from an incomplete deinactivation of the As conductance between successive episodes of discharge, which decreases its inhibitory effect, accounting for the time-dependence observed (Fig. 7A). At the biophysical level, this effect arises because the time constant of inactivation is smaller at depolarized potentials (rapid inactivation) than at hyperpolarized potentials (slow deinactivation; see [32]). This is essential as different voltage-dependence of the inactivation time constant in neocortical neurons yields temporal properties of the discharge that present strong differences in their logic (see next

section). In SONs, successive episodes of depolarizing inputs ("UP states") progressively inactivate the As conductance and therefore facilitate the response to subsequent inputs. In this manner, phasic synaptic events are not explicitly memorized under the form of self-sustained activity. Rather, the effect of successive synaptic inputs separated in time progressively cumulate through the slow dynamics of a hidden variable. In this manner, the As conductance of SONs is strategically situated to exert a cardinal role in the temporal integration of asynchronous inputs converging from distinct cortical areas that is required in learning and producing adapted behavioral responses [33]. In particular, it may participate to the slowly-developing responses anticipating behavioral response and predicting forthcoming rewards [34].

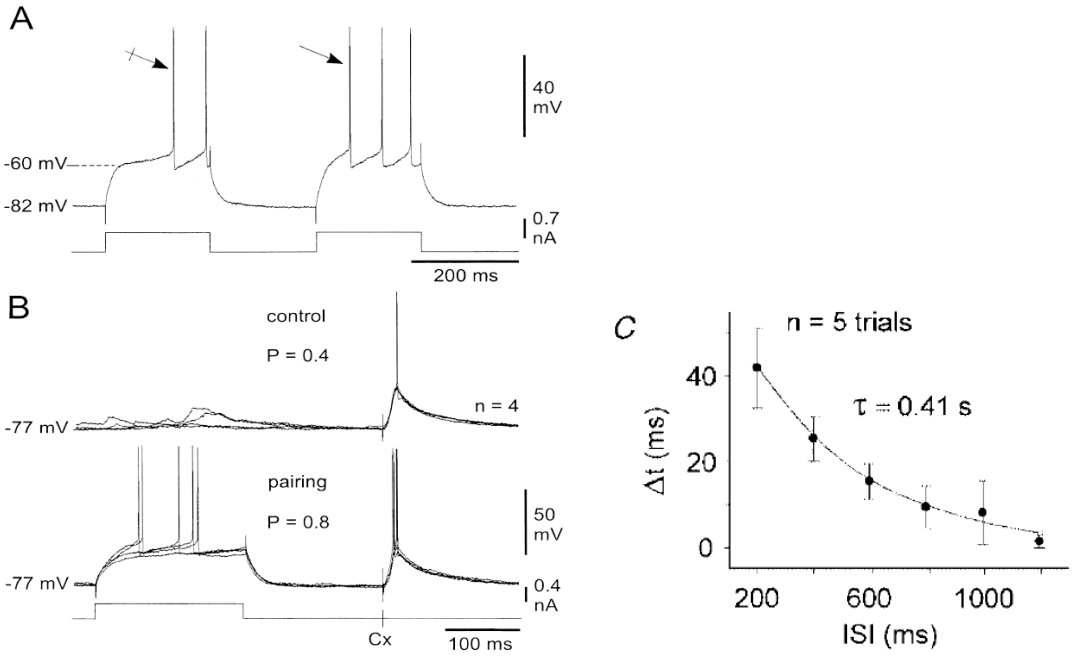

Fig. 6. A. Latency-to-first-spike reduction in response to two successive inputs *in vivo*. **B.** Increase of the spiking probability in response to threshold cortico-striatal inputs after a direct injection of depolarizing current *in vivo*. **C.** Time-dependence of the latency-to-first-spike reduction as a function of the inter-stimulus interval between successive inputs (adapted from [3,4]).

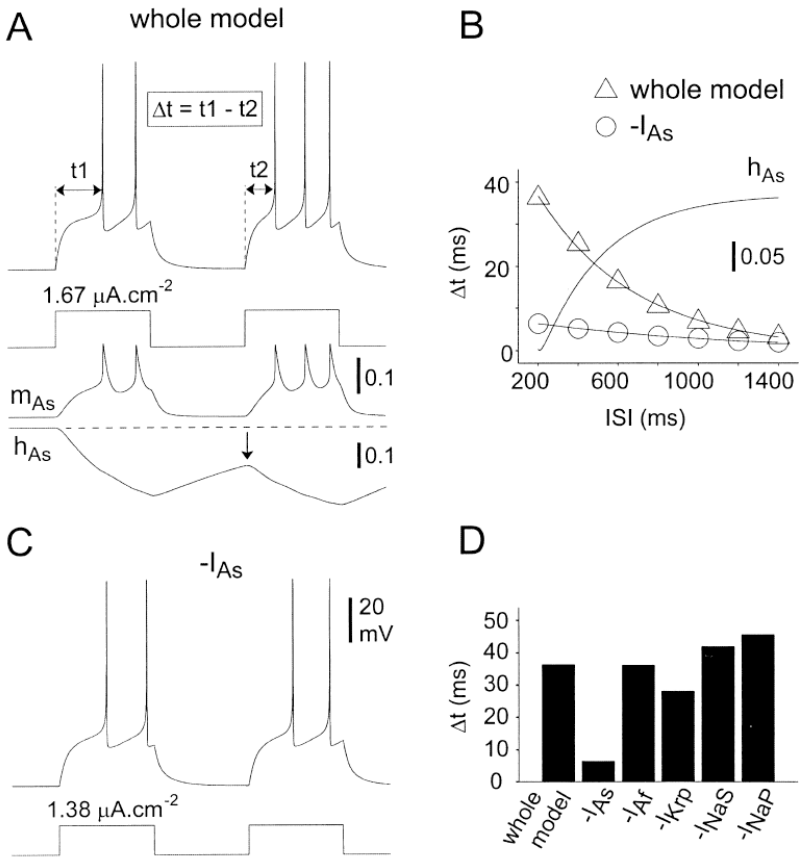

Fig. 7. A. Reduction in latency-to-first-spike in the SON model. **B.** The reduction is absent when IAs is removed. **C.** Time-dependence of the latency-to-first-spike reduction in the model. **D.** Reduction in latency-to-first-spike in the SON model in the whole model and when different voltage-gated conductance are removed (from [3])

5. Memory of inhibition and the control of ramp discharges by Ks conductance in cortical neurons

Cellular forms of short-term memory induced by slowly-inactivating outward conductance are actually ubiquitous to many cellular types, in invertebrates and vertebrates (in the following, we use Ks to generically denote such conductance. The primary effect of Ks conductance is to prolong the latency-to-first-spike in response to current steps, i.e. one or two order of magnitude larger than the usual period of spiking [22]. This property is due to a *memory of inhibition*. Specifically, a transient hyperpolarization of the neuron de-inactivates the Ks conductance (i.e. increases the inactivation variable); because it inactivates slowly, Ks opposes subsequent depolarization for finite durations, i.e. of the order of 0.1 to 10 s, depending on its time constant and the input current amplitude. By opposition, some neurons, as SONs, also display a *memory of excitation*: a period of depolarization inactivates the conductance and increases the response of the neuron to subsequent inputs because deinactivation of the conductance is slow during hyperpolarized period between depolarizing inputs (e.g. [3,4,22,35]). Indeed, as noted in the previous section, memory of excitation requires that the time constant of inactivation at hyperpolarized potentials is slow (slow deinactivation), compared to that at hyperpolarized potentials (rapid inactivation), as in SONs. To the contrary, memory of inhibition requires slow inactivation and rapid deinactivation, as can be found in neocortical pyramidal neurons [36].

In memory of inhibition, the amplitude of a transient inhibitory input determines the amount of deinactivation and thus latency-to-first-spike. This mechanism represents an interesting possible form of temporal computation, as a phasic input can control the forth-coming discharge pattern of a neuron at a time scale that is behaviorally relevant. Together with Dr. E. Guigon, we have addressed the issue of whether this mechanism is likely in behavioral conditions *in vivo*, where cortical neurons are driven by background asynchronous synaptic inputs and operate within local network architectures [37]. In particular, we have shown that latency-to-first-spike is not a highly variable temporal property in single neurons in the presence of noisy synaptic inputs (Fig. 8), whereas it represents a reliable feature in output neurons of convergent architectures (Fig. 9). However, in recurrent architectures, which are canonical in cortical micro-circuitry, we found that there was no significant latency-to-first-spike anymore (Fig. 10). Rather, spiking started immediately in the network and a ramp pattern of discharge emerged with a near-to-linear increase in frequency. Moreover, we found that the initial inactivation, which can be controlled by physiological inhibitory inputs, determined the slope of this ramp [37]. Remarkably, these properties rely on

detailed biophysical properties of the Ks conductance considered, i.e. the voltage-dependence of time constant of the Ks conductance, which is specific to neuronal types.

Thus, these results indicate that an electrophysiological property such as the latency-to-first-spike may express very differently *in vivo*, compared to its appearance *in vitro*. Moreover, it shows that depending on the architecture in which it expresses, it may offer different forms of temporal computation. In behaving animals, the ramps we have observed are ubiquitous in sensorimotor and cognitive processes such as sensory integration, decision-making, response anticipation or reward expectation [38,39,40]. Interestingly, neurons that display such ramping activity in behavioral conditions also show marked phasic silence before the ramp [41]. We suggest that ramping activities may rely in part on the capacity of local assemblies to generate frequency increases at rate controlled by previous inputs through the memory properties conferred by Ks. As an alternative possibility, ramping activities may arise from slow NMDA synaptic interactions in recurrent neural networks [42].

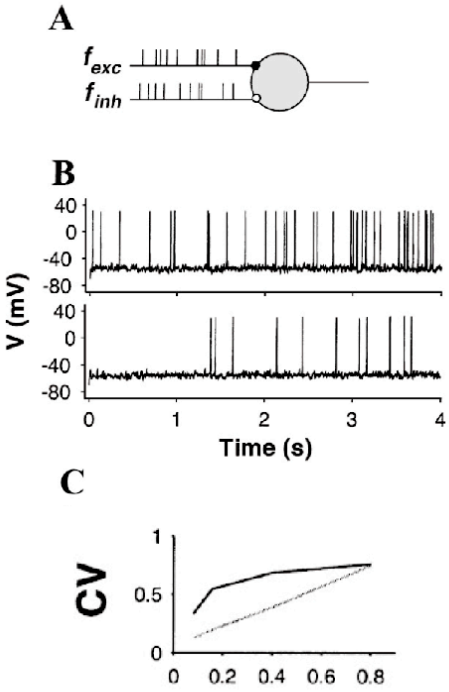

Fig. 8. A. A neocortical neuron model submitted to noisy excitatory and inhibitory inputs. **B.** The latency-to-first-spike is highly dependent on membrane fluctuations resulting from noisy inputs because the depolarization preceding the first spike is just sub-threshold. **C.** Latency-to-first-spike is therefore not reliable, with $cv > 0.5$ (black curve; adapted from [37]).

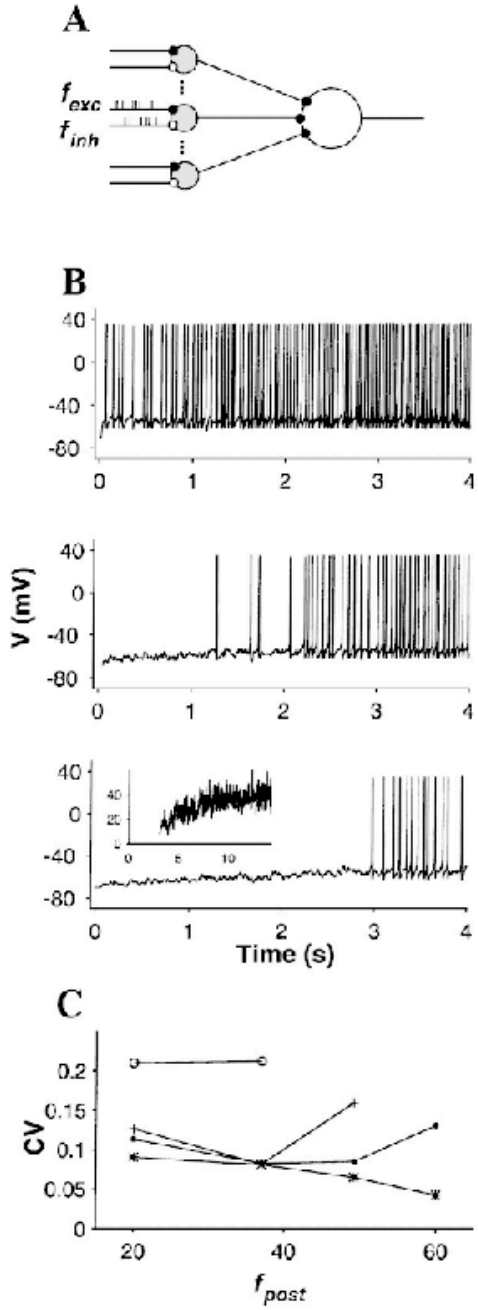

Fig. 9. A. Feed-forward architecture of neocortical neurons endowed with the Ks conductance converging on an output neuron. **B.** Latency-to-first-spike in the output neuron depends on the initial level of deinactivation. **C.** Latency-to-first-spike is reliable, i.e. with $cv \sim 0.1$ (Adapted from [37]).

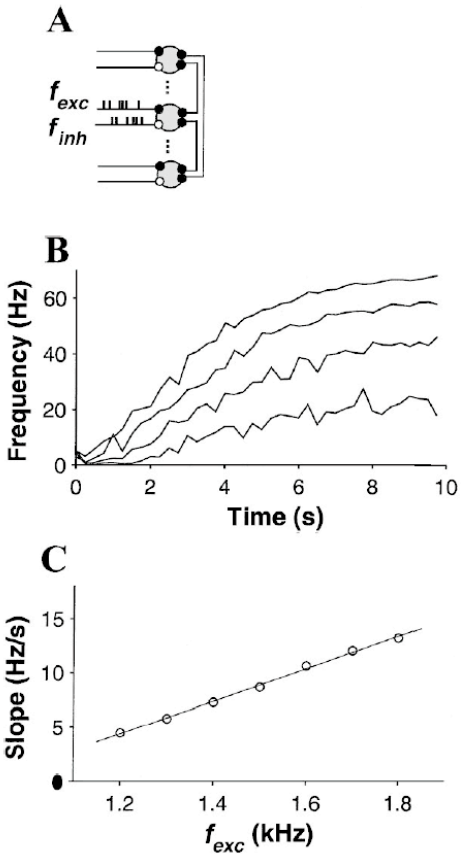

Fig. 10. A. Recurrent architecture of neocortical neurons endowed with the Ks conductance. **B.** Latency-to-first-spike is null and a ramp of discharge emerges with a near-to-linear increase in frequency. **C.** The slope of this ramp depends on the initial inactivation level and on the frequency of external excitatory inputs (adapted from [37]).

6. Plateaus and valleys in Purkinje cells (PC)

In collaboration with Dr. S. Genet, I have been studying short-term memory in Purkinje cells (PCs), which display some similarity with the computational properties provided by slowly-inactivating potassium conductance (see previous sections), although they rely on very different biophysical grounds [6,7].

PCs dendrites present the ability to fire calcium (Ca) spikes upon strong depolarizing stimuli [43], underlying the so-called "complex spike" evoked by activation of the climbing fiber (CF). They also can fire plateau potentials, which are threshold events of low-amplitude depolarization (~15 mV) and long duration (~0.1-1s; [44]). Plateaus putatively participate in dendritic computations and synaptic plasticity but these roles have remained obscure as models were unable to account both for their finite duration, their threshold behavior and the order of relative thresholds between Ca spikes and plateaus (e.g. [45]). We have built a model to investigate the minimal biophysical properties required to produce the dual electro-responsiveness of PC dendrites [7]. The model shows that plateau potentials and calcium spikes can both be generated by the same set of underlying currents: the P-type Ca current, a delayed rectifier K current and a sub-threshold, generic K current that lumps together a set of low-voltage activated K currents described in PCs [7]. Indeed, a bifurcation analysis (Fig. 11A) demonstrated the model ability to both account for the double excitability of PC dendrites, with Ca spiking emerging at large input currents (Fig. 11B) and plateaus arising at lower currents in a region (Ω) were the membrane potential is bistable. In the Ω region, the dendrite could be switched between its stable up and down states (not shown), possibly accounting for the quasi-stable plateaus observed by [43]. Below Ω, the model demonstrated the existence of finite duration plateau potentials, which accounted for the shape and cardinal properties of those observed experimentally in PCs (Fig. 11C; [44]). Moreover, above Ω, our simulations predicted the existence of mirrors events of plateaus that we have termed valleys and that have been experimentally observed since, with similar properties [46].

Specifically, in the vicinity of the Ω region, the derivative field is distorted as it parallels the fixed point branches of the system: depolarization from the resting potential (below Ω) or hyperpolarization from the plateau potential (above Ω) thus occur at low voltage derivatives, which account for the possible long finite duration of plateaus and valleys (Fig. 11E), even in a model where all other dynamical variables are assumed at their equilibrium (thin lines in Fig. 11C and D). Thus, slow dynamical behaviors can arise for topological reasons, related to the bifurcation diagram, rather than from the order of

magnitude of a time constant.

From a functional viewpoint, this behavior may be cardinal because 1) the duration of plateaus and valleys is a function of the amplitude of the constant current mimicking background asynchronous synaptic inputs (Fig. 11F), 2) a multi-compartimental version of our model suggests that plateaus and valleys are robust events that invade the whole dendritic tree and determine epochs of somatic firing and silence of PC (Fig. 12; [6]). Hence, periods of spiking and silence (pauses) may be triggered by the climbing fiber (Fig. 12A, C and E), parallel fibers (Fig. 12B and F) and stellate cells inhibitory inputs (Fig. 12D and F) in a stable toggle mode (Fig. 12E and F) or for finite duration controlled by the level of asynchronous background synaptic inputs (Fig. 12A and F). Thus, we suggest that plateaus and valleys may constitute the mechanisms allowing temporal patterning of PCs activity, which is essential to motor control, as these neurons represent the sole output stage of the cerebellum.

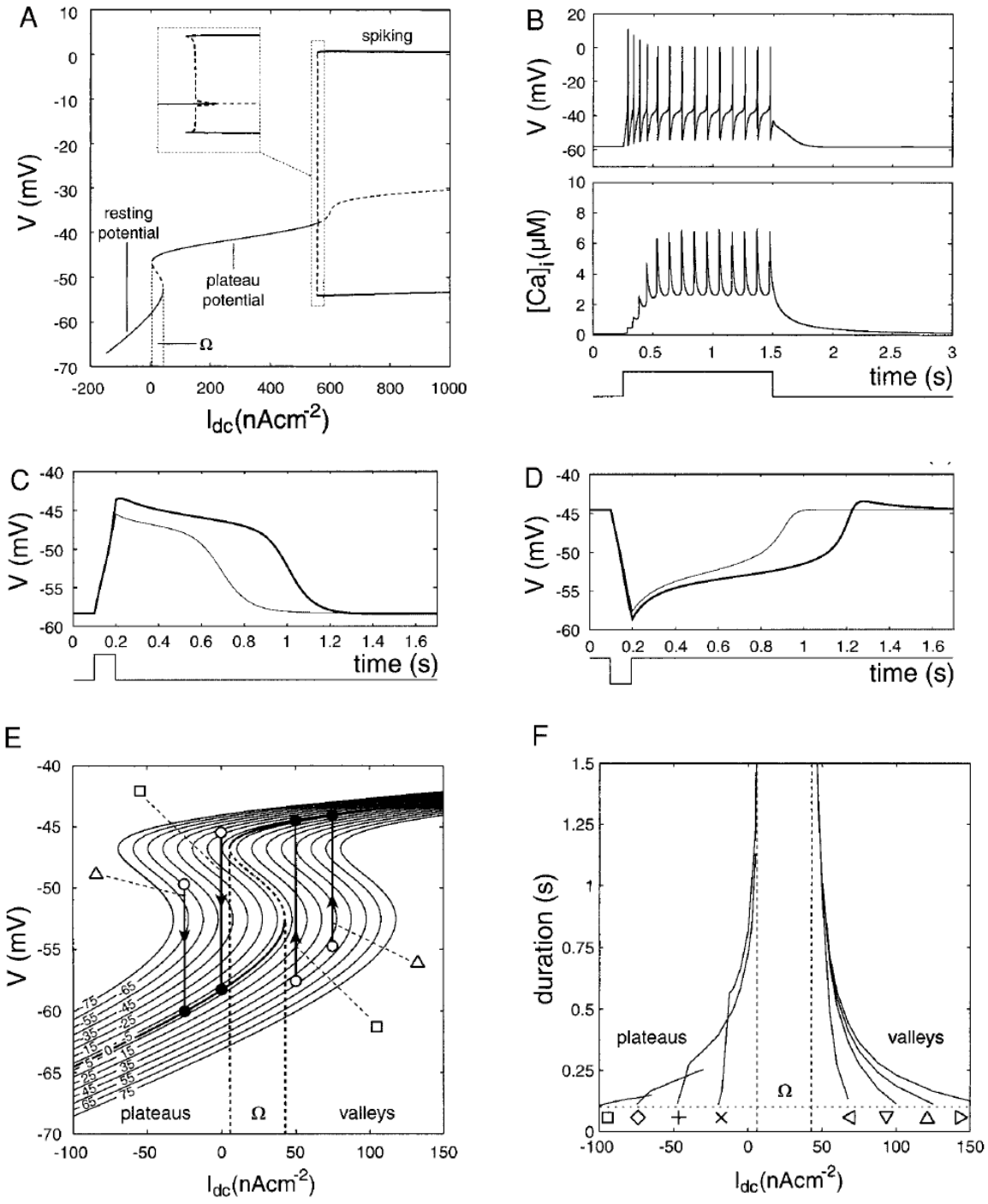

Fig. 11. A. Bifurcation diagram of the dendrite PC model; bistable region: Ω. **B.** Calcium spiking at large injected currents. **C.** Finite duration plateau in the full model (bold line) and 1-D reduction (thin line). **D.** Example of a valley in the full and 1-D models. **E.** Bifurcation diagram and derivative isoclines in the Ω region. Relaxation of plateaus and valleys: straight lines oriented downward and upward, respectively. **F.** Durations of plateaus and valleys as a function of the constant injected current (adapted from [7]).

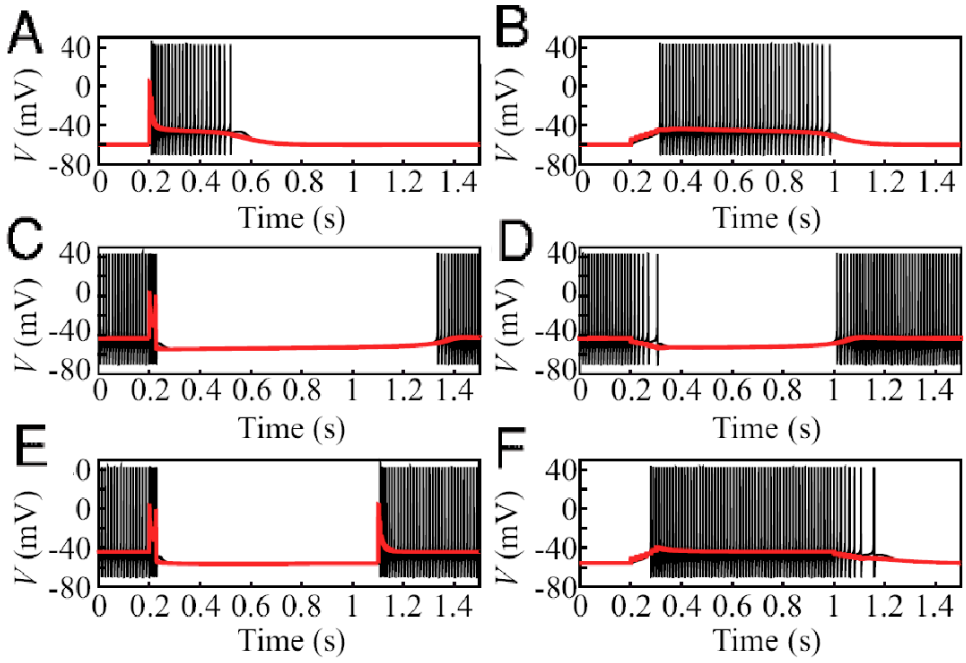

Fig. 12. A. Dendritic finite duration plateau (red line) and somatic sodium spiking (black line) triggered by climbing fiber (CF) activation from the resting state. **B.** Similar events triggered by parallel fiber (PF) activation. **C.** Dendritic finite duration valley and somatic spiking pause triggered by CF activation from the plateau state. **D.** Similar events triggered by stellate cells (SC) activation. **E.** Alternating epochs of somatic spiking and pause resulting from dendritic switches between stable plateau and valley triggered by successive CF inputs. **F.** Similar events induced by successive PF and SC inputs (adapted from [6]).

7. A new principle for activity-dependent plasticity and memory

Several mathematical models have addressed the potential contribution of KP cycles to the induction of plastic modifications in neurons, including models of long-term potentiation (LTP) and depression (LTD). In these models, KP cycles control the strength of the excitatory synapse via the number of AMPA receptors [47,48,49,50,51]. These models predict that the direction (e.g. increase) of synaptic modifications depends on calcium concentration, consistent with empirical observation [52,53,54]. However, they fail to provide explanatory mechanisms for the maintenance of these modifications. In another class of KP cycle models, bistability of the phosphorylated substrate fraction arises from positive feedback in some KP cycles, yielding binary information storage [55,56,57,58]. In particular, auto-activation of the Ca2+/calmodulin-dependent protein kinase II (CaMKII) may underlie all-or-none LTP at individual CA3–CA1 hippocampal synapses [59]. However, some forms of synaptic plasticity imply implicates other KP cycles devoid of auto-activation [60,61] and display gradation at individual synapses [62,63,64,65], as synaptic scaling of individual synapses [66,67,68,69,70,71] and intrinsic plasticity [18,72], which cannot be explained by bistable models. Moreover, CaMKII models present slow rising kinetics (minutes to days) [57,58] that is inconsistent with the rapid induction of plasticity observed experimentally (e.g., [18,63,73,74,75]) and do not account for LTD induction at intermediate calcium levels that characterize synaptic and intrinsic plasticity [53,54,76]. Finally, the implication of CaMKII itself in the maintenance of synaptic information is in fact strongly challenged [77,78,79]. Most probably, information storage in neurons does not, therefore, rely exclusively on the bistability of auto-activating KP cycles. Indeed, most KP cycles involved in learning and memory are devoid of auto-activation, but share the common feature of being activated by upstream signals that reflect neuronal activity. Such activity-dependent KP (aKP) cycles are ubiquitous and include most major kinases (e.g. PKA, PKC, MAPK) and phosphatases (e.g. PP1, PP2A, and PP2B).

We have assessed, with Dr S. Genet, the performance of generic aKP cycles in information storage [8]. Our results show that aKP cycles account for both induction (plasticity) and maintenance (memory) of synaptic or intrinsic modifications in neurons, through a single activity-dependent process controlled by activity. In its macroscopic determinist approximation, the model consists of a simple reaction scheme. The non-phosphorylated (S) and phosphorylated (S*) forms of the substrate are present with fractions

$1-f$ and f, respectively, and are inter-converted with rates K and P by a kinase and a phosphatase; enzymes are activity dependent through calcium, and f is the readout variable (Fig. 13A). Consistent with experimental observations, plasticity induction is rapid, bidirectional (Fig. 13B), and graded (Fig. 13C), with information storage up to 6 bits, e.g. for the regulation of a somatic intrinsic conductance. Moreover, long-term maintenance of plastic modifications is reliable (even in spines where stochastic molecular fluctuations are maximal) and robust to the passage of time, with memory ranging from short to long term, depending on the biophysical properties of the model, thanks to the activity-dependent time-constant that emerges from the control of reaction kinetics by calcium (Fig. 13D). In the presence of molecular turnover, the duration of aKP memory is limited by the time constant of turnover. This limit in turn depends on the substrate, but can increase up to weeks [50]. As an extension to our model, we have implemented a speculative mechanism originally proposed by Crick [80] to quantitatively evaluate its protective action on memory. We show that this mechanism efficiently restores memory timescales that are compatible with animal and human memory even in the presence of molecular turnover. Finally, the aKP model predicts that plastic modifications reflect the instantaneous rate of KP cycles operation rather than their steady state in opposition to previous models of plasticity induction [47,48,49,50,51,81,82] and accounts for activity-dependent modifications of hippocampal and cortical synaptic weights (i.e. the theoretical ‘‘BCM’’ rule) [53,54,83], or of intrinsic properties [18,76].

As an important application, the aKP model is the first one, to our knowledge, to provide a biophysically realistic theoretical framework describing the plastic rules underlying intrinsic plasticity in neurons (*IP rules*, which form a causal loop with *IP effects*, see **Part 8**). Indeed, strong experimental evidence indicates that electrical activity activates a variety of kinase and phosphatase (KP) cycles (e.g. PKA, PKC, CaMKII, calmodulin) through calcium signaling, to determine the density and regulatory state of ionic membrane channels (e.g. [73]). Remarkably, the regulation of conductance through IP generally appears to be a graded process (e.g. [18,76]). Furthermore, anti-homeostatic forms of IP, which are commonly thought as possible candidate for information storage and behavioral learning display rapid induction (i.e. seconds time-scale) relative to homeostatic IP (i.e. hours to days; [84]) and maintenance is long-term [85]. Thus, because it displays graded plastic modifications, fast induction and long-term maintenance thanks to its activity-dependent time constant, the aKP model provides a coherent framework to build IP rules that appear more biophysically realistic than previous models [19,86,87,88,89].

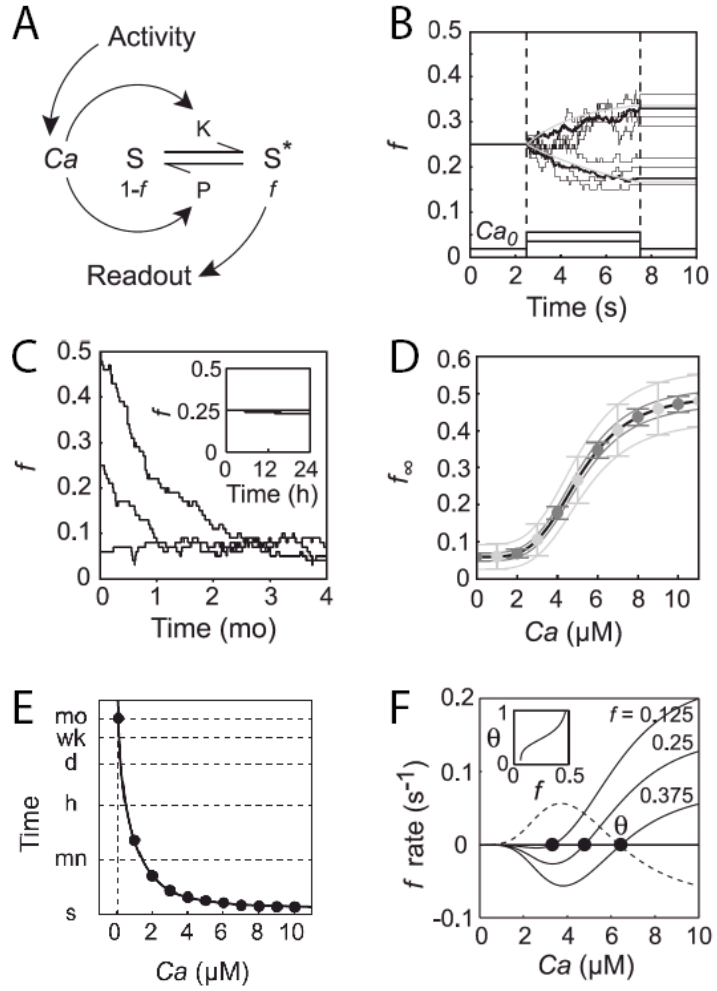

Fig. 13. A. Scheme of the macroscopic version of the model (see text). **B.** Induction of rapid, bidirectional plastic modifications of f in response to micro-molar calcium stimulation. **C.** Long-term relaxation of f at basal calcium from different initial conditions. **D.** The steady-state phosphorylated fraction, f^*, is a graded function of calcium in the deterministic (thick black line) and stochastic versions of the model (circles; number of substrate molecules is 500 [dark gray] and 50 [light gray]). **E.** The time constant of f, τ_f, as a function of calcium in the deterministic (line) and stochastic model (black dots). **F.** f rate versus calcium in the deterministic model. Inset: modification threshold θ versus f (adapted from [8])

8. Intrinsic plasticity (IP) effects

Intrinsic plasticity (IP) is a ubiquitous activity-dependent process regulating neuronal excitability and a cellular correlate of behavioral learning and neuronal homeostasis. Because IP is induced rapidly, maintained long-term and determines the propensity of neurons to discharge, it likely represents a major determinant of adaptive collective neuronal dynamics. IP involves a causal loop between neuronal electrical activity and the regulatory state of membrane ionic channels. Indeed, activity-induced signaling pathways modify the biophysical/biochemical channel apparatus, a process commonly referred to as *IP rules* (see Part 7). In turn, the state of ionic channels determines the level and pattern of neuronal activity in response to ongoing network synaptic inputs, a causal dependence that we term *IP effects*. Assessing the exact impact of IP has remained elusive. Indeed, it is extremely difficult disentangling the complex non-linear interaction between IP effects, by which conductance changes alter neuronal activity, and IP rules, whereby activity modifies the conductance state via signaling pathways. Lately, I have developed a program to study IP effects, both experimentally in cortical neurons *in vivo*, with S. Charpier, S. Mahon and J. Paz (ICM, Paris, France) and through analytical and simulations of neuron and network models with my Ph.D. student J. Naudé (ISIR, Paris, France). This program is part of a global strategy aimed at gaining separate generic theoretical descriptions of IP effects and IP rules to be combined into a generic framework in order to get a tractable analysis and a global picture of the IP loop.

In neocortical neurons, we have demonstrated, analyzing *in vivo* intracellular recordings in the rat that the intrinsic excitability of two-thirds of layer V pyramidal neurons is altered following brief periods of repeated firing mimicking motor learning [11]. Moreover, the modifications observed display a great variability, as neurons expressed modifications of the gain (Fig. 14A and B) or the threshold (Fig. 14C and D) of the frequency-current ($f-I$) relation, or both. Moreover, these modifications could be bidirectional (Fig. 14E and F). Thus, this study demonstrated that *in vivo*, IP effects exhibit an impressive diversity, even within a homogenous population of neurons, which encompasses the variability of IP effects observed *in vitro*.

With J. Naudé, we have developed an extensive theoretical analysis of IP effects, in order to enlighten the mechanisms underlying threshold and gain modulation that are observed empirically. To that end, we have achieved an extensive exploration of threshold and efficacy (the inverse of the $f-I$ relation gain) sensitivities in a single compartment model of a regular spiking neuron model embedded with a generic voltage-dependent

conductance, in order to explore the effect on modifications of its maximal conductance on the $f-I$ relation (Fig. 15 A-D). Exploration of the principal directions of the parameter space demonstrates the presence of two contiguous domains of elevated threshold or efficacy (inverse gain) sensitivities that marginally overlap (Fig. 15 E and F). This topology is found systematically, across all combinations of the reversal potential, activation and inactivation kinetics tested. On the one hand, conductance that activate sub-threshold, i.e. which activation is essentially independent of the occurrence of spikes, display high threshold sensitivities so that modifying their maximal conductance strongly affect the $f-I$ threshold. On the other hand, conductance activating supra-threshold, i.e. in correlation with spikes, present high inverse gain sensitivities; modifying these conductance affect the gain of the f-I. Analyzing equivalent integrate-and-fire models, we derive analytical expressions of IP effects that relate to conductance biophysical parameters, unravel the specific mechanisms by which activation governs threshold and gain modifications, and provide an analytical criterion separating the corresponding domains. Finally, we demonstrate that our results generalize to IP of other voltage-dependent conductance parameters and allow strong inference on IP of calcium-gated conductance. Of particular importance, the results we obtain are independent of the rules that actually govern IP (e.g. homeostatic versus non-homeostatic IP), at odds with current parameter robustness analysis of excitability, which rely on homeostatic regulation of conductance (e.g. [90,91,92]). The theoretical expressions of IP effects we have gained can be combined with IP rules in rate or spiking neural network models, offering a realistic and tractable framework to systematically assess the dynamical and computational consequences of the IP loop.

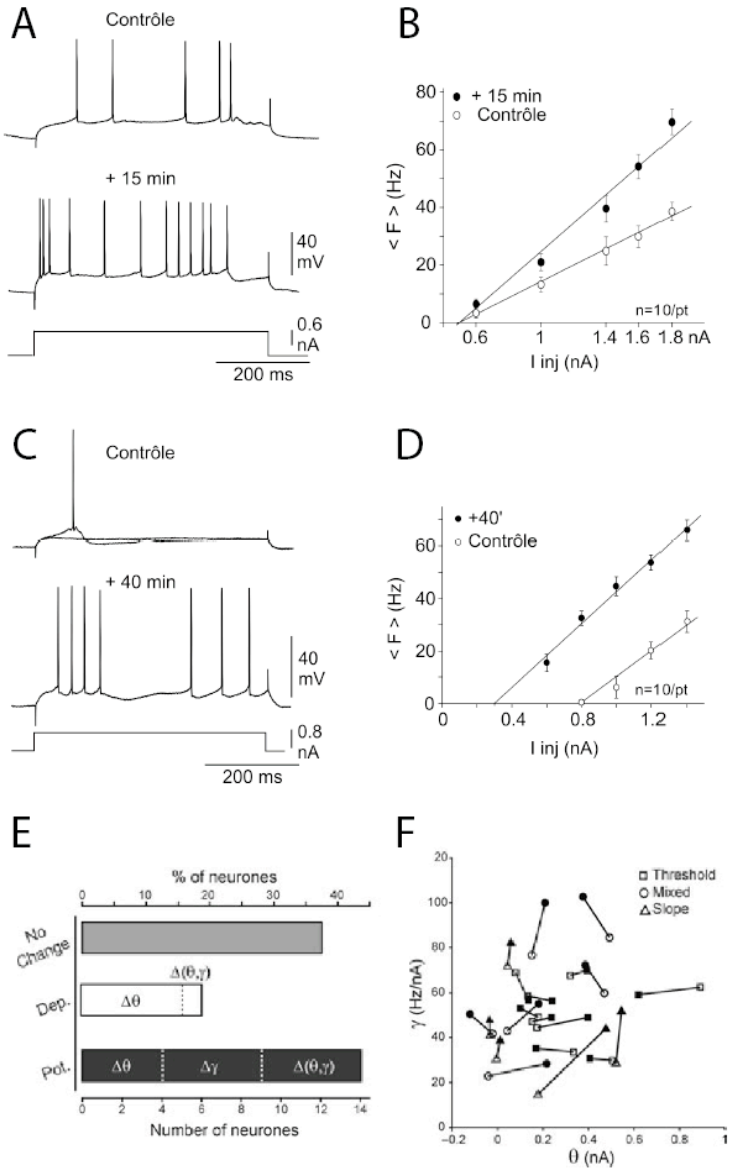

Fig. 14. A. Firing of a layer V pyramidal neuron of the motor cortex to the same depolarizing pulse before and after application of the conditioning protocol. **B.** In this neuron, the gain of the $f-I$ relation was increased by the conditioning protocol. **C.** Firing before and after application of the conditioning neuron in another neuron. **D.** In that neuron, the threshold of the $f-I$ relation was decreased. **E.** Classification of the diversity of changes in the $f-I$ relation. **F.** Quantification of the diversity of changes in the $f-I$ relation (adapted from [11]).

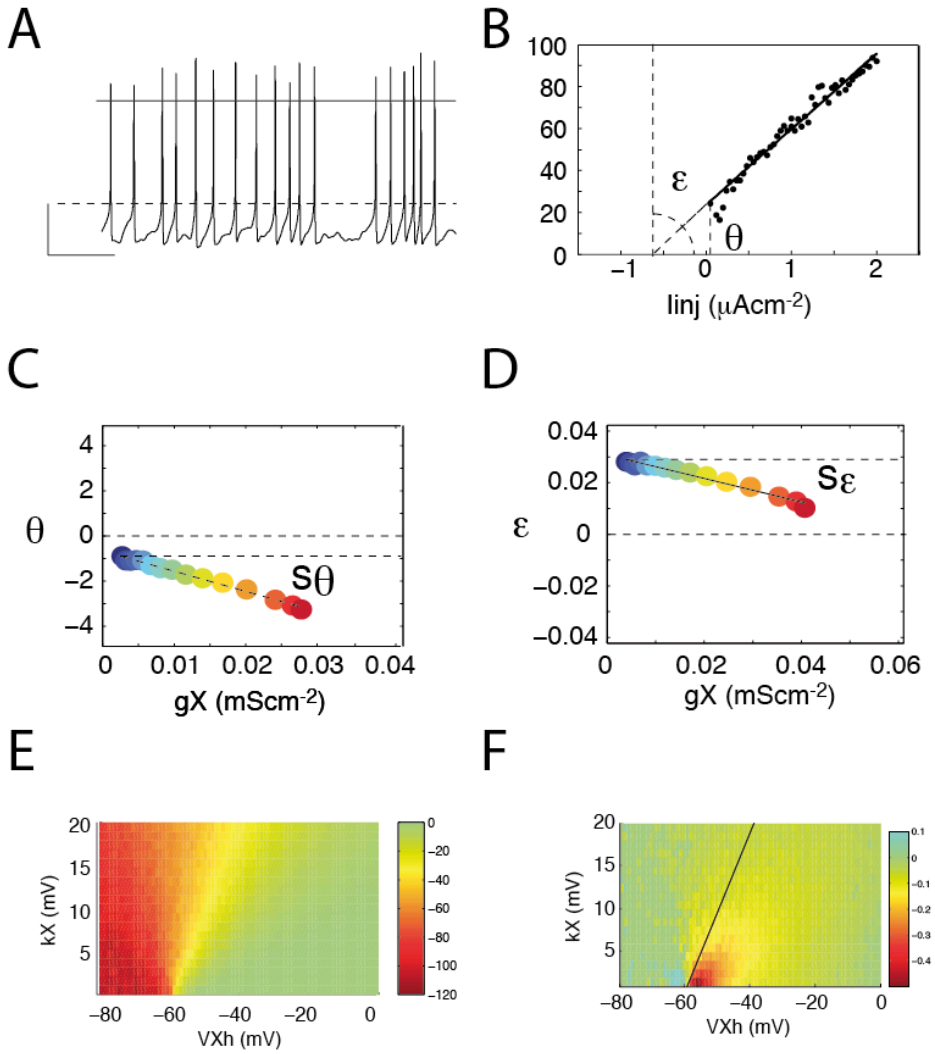

Fig. 15. A. Typical membrane potential in response to a constant input current and random background synaptic current. Bars 20 mV, 100 ms. **B.** Typical $f-I$ relation. The current threshold for spiking, θ is defined as the first current eliciting yielding firing. The inverse gain, ε, the inverse of the $f-I$ gain, γ, was estimated from linear regression. **C.** Estimate of s_θ, the threshold sensitivity, from the linear dependence of the threshold for spiking, θ, as a function of g_X. **D.** Similar estimate of s_ε, the inverse gain sensitivity. **E.** Threshold sensitivity map of the model (sodium conductance), s_θ as a function of the half-activation potential (V_{Xh}) and e-fold slope of the Boltzmann activation voltage-dependence (k_X). **F.** Inverse gain sensitivity s_ε map of the model (adapted from Naudé et al., *in revision*).

9. Project

1. Long-lasting firing patterns and behavior

Cardinal animal and human cognitive abilities such as perceptual integration, decision-making, motor coordination or working memory are actually strongly structured in the time domain at the behavioral time-scale range (i.e. 0.1-10 s). Empirical evidence indicates that these functions correlate with a variety of common long-lasting neuronal activities in many central brain structures (e.g. cortex, hippocampus, basal ganglia, cerebellum), which includes persistent firing, ramping, decaying or non-monotonous patterns [93].

Persistent firing and ramping represent landmark activity patterns and have been studied the most because they are widely considered underlying two complementary cardinal aspects of temporal computation at the behavioral time scale. Persistent neural activities (or *delay* activities) constitute self-sustained selective traces of past stimuli (*retrospective* memory; [13]). Ramping activities integrate continuous on-going neuronal inputs into a - generally linear - increasing firing frequency pattern that can in principle underlie neuronal computations such as counting, timing or anticipating events. Ramping can thus serve a form of *prospective* memory, because it can encode prediction of forthcoming sensory events or rewards or future decisions or actions [38,39,40]. Thus, persistent firing and ramping represent complementary ways to solve the core issue of temporal computation at the behavioral time scale: bridging events separated in time (i.e. past and present events for persistent firing and present and future events for ramping).

Empirical evidence strongly suggests that persistent or ramping patterns actually reflect neural computations mechanistically responsible for cognitive functions structured in time. For instance, it has been shown that the occurrence or absence of selective continuous delay activities correlates, on a trial-to-trial basis, with the correct or improper execution of the behavioral response [94]. Similarly, decoding impending actions can be achieved from the firing pattern of as few as 4 to 5 neurons firing during a delay period, even when considering only discontinuous delay firing neurons [95]. Therefore, unraveling the mechanisms of temporal firing patterns likely represents a key step in understanding major cognitive functions that are structured in time. Moreover, because they are shared by many functions and widespread across the brain, persistent firing or ramping likely represent universal forms of circuit dynamics, raising incentive for studying their mechanisms.

2. Current theories of long-lasting neuronal activities

In the following, we focus on persistent activities. Ramping activities are commonly considered to operate downstream of persistent activities through integration, by mechanisms that are still debated (see Part 4). Numerous theoretical studies have addressed the mechanisms underlying persistent neural activity and unraveled several cardinal dynamical features that characterize this firing pattern [93,96]. As a central result, it has been largely demonstrated that selective persistent neuronal activity can be triggered by transiently stimulating a sub-set of neurons in a recurrent network model spontaneously discharging at low-rate [28]. This result matches well the behavior observed in neurons engaged in object working memory in the frontal or inferotemporal cortex, where selective delay activity encode the presence and identity of a visual object [13]. From the perspective of dynamical systems, there is bistability i.e. two stable states co-exist, the low frequency spontaneous state and the higher frequency persistent activity state. The existence of the persistent activity is primarily ensured by activity reverberation requiring a strong excitatory feedback, as it was long been hypothesized since Hebb. Obviously, a mechanism to control run-away excitation is essential and can be provided by synaptic inhibition [97,98] or saturation of the input-output function [99]. In particular, at low-frequency spontaneous firing (<5Hz) requires the network to be dominated by inhibition in baseline conditions [100]. Inhibition is also crucial for the selectivity of persistent activity, because neurons selective of a stimulus engaged in a persistent firing inhibit neurons selective to other stimuli, preventing them to enter the persistent activity [96]. Besides, in the persistent state, asynchronous firing is important because synaptic potentials have shorter characteristic times than the average inter-spike interval during persistent activity (typically 20-50 ms). However, it has been shown that the longer decay time-constant of $GABA_A$ synaptic currents, relative to that of AMPA currents, renders persistent activity unstable through the development of synchronized oscillations [101]. Many models have shown, however, than the presence of NMDAR-mediated transmission allows avoiding this situation [101]. Although empirical and theoretical studies now form a consistent corpus that point toward the plausible existence of bistability in recurrent neural networks, a number of cardinal issues still remain unanswered with regard to the dynamics, statistics and plasticity of long-lasting activities.

3. Robustness of graded persistent activity

Strong experimental evidence indicates that *graded* persistent activity, which is thought to be the neural substrate of the short-term memory of analog values, is widespread [41]. In terms of dynamical systems, graded persistent activity corresponds to the co-existence of multiple attractors, i.e. multistability. In the ideal case, the analogue value is encoded with infinite precision, which requires an infinite number of stable fixed-point attractors that coalesce in a single *line attractor*. It has been shown that recurrent neural networks can reproduce a line attractor, but at the inevitable price of fine numerical tuning of parameters (see e.g. [102,103]). In particular, realistic persistent firing rates close to the spontaneous firing rate require inhibition that reduces the robustness of multistability [101,104]. Overall, synaptic weights have to be tuned to within typically 1% or less, which corresponds to unrealistic biological levels of regulation. In a similar way, "bump attractors", which are thought underlying spatial working memory under the form of location-specific persistent discharges (i.e. line attractors in space rather than in value) require very strong assumptions on the synaptic structure (matrix) of recurrent networks [29,96,105,106]. In reaction, the possibility has been studied that recurrent neural networks may *only* approximate perfect line attractors under the form of a large number of co-existing discrete attractors, such as in networks of bistable elements (e.g. neurons or local circuits; [105,107,108]). However, there currently exists no fine-grained biophysical implementation of this principle, which would be essential to assess its plausibility. Thus, the way brain structures are able to maintain graded levels of persistent activity remains a debated issue and there is currently no standard model that account for all the properties of this essential type of dynamics.

4. Statistics of persistent activities

Models of working memory are also strongly challenged because they systematically predict larger firing variability (as measured by their coefficient of variation) during spontaneous firing, as compared to persistent firing, exactly the opposite of the situation observed experimentally [109]. This is so in recurrent model networks because the balance of inhibition and excitation, which ensures significant firing frequency fluctuations in the regime of low rate spontaneous discharge, is lost when excitation dominates during persistent activity at higher rates [96]. A model has been proposed where the balance between excitation and inhibition is preserved at higher rates, but it requires fine-tuning of parameters [110]. Also, it has been shown that high reset potentials combined with short-term synaptic depression

allows higher variability of the persistent activity in a bistable recurrent network. However, this study accounts only for a fraction of the difference in variability observed experimentally and precisely depends upon the details of synaptic depression [111]. Thus, accounting for the increased variability during persistent activity remains an open issue that currently challenges neural network models based on recurrent activity.

5. Plasticity of persistent activity

Empirical evidence largely demonstrates that persistent or ramping activities in associative cortices or the striatum, e.g., display set up, extinction and magnitude dynamics that parallel changes in contingencies or the behavior itself within a few (often one) trial(s) [95,112,113]. This is not to be surprising because these areas are typically highly implicated in the remarkable ability to form and rearrange arbitrary associations rapidly, especially in primates. Several theoretical studies have shown that Hebbian synaptic plasticity can structure the connectivity of recurrent neural network models to provide sufficient reverberation in subsets of associated neurons and induce selective persistent retrospective activities [114,115]. In a similar way, it has been shown how prospective activities can emerge from Hebbian synaptic association between retrospective persistent activities and choice stimulus activity [116]. However, these studies typically predict that >10 to hundreds of trials are required for the emergence of memory activities [114,115,116]. These studies are based on coarse-grained descriptions of the biochemical and biophysical processes underlying long-term synaptic plasticity. The question thus currently remains unanswered as whether synaptic plasticity is actually responsible for the fast arbitrary associations rearrangement that are observed experimentally, or whether other forms of plasticity are implicated. The study of neural network models with fine-grained descriptions of plasticity rules would allow enlighten this issue.

6. The intrinsic hypothesis

Parts 2-6 describe a set of cellular short-term memory mechanisms that are summarized in Table 1. The remarkable property of neuronal multistability that allows neurons to display a graded set of stable firing frequency and which depends on calcium-activated slow inward currents and has been observed in spinal and cortical neurons may be added to that list [18,117]. Major common properties emerge from this comparison. All these mechanisms operate at the time-scale of behavior, i.e. 0.1-10s typically. They are triggered by phasic

inputs, i.e. of the order of the second or less, and their expression (i.e. duration, rate) is controlled by the tonic level of background synaptic inputs. In this manner, transient barrages of synaptic activity signaling salient behavioral (sensory, motor or cognitive) events can be transformed into firing patterns that prolong their influence much longer than membrane or synaptic decay time constants (typically ~ 10 ms).

	Mechanism	*Code*	*Time scale*	*Induction*	*Control*	*Conduct.*	*Architecture*	*Structure*
Sustained discharge	bistability	frequency	s-mn	phasic	tonic	NaP, Ca	FF recurrent?	Cx, SC
OFF transition	activation summation	binary	0.1 s	phasic	frequency of sust. disch.	Ks, AHP	FF recurrent?	Cx
Integration	$\tau_{INACT} < \tau_{DEINACT}$	frequency	s	separated phasic inputs	tonic + phasic hyper.	Ks	FF recurrent	Str
Latency-to-first-spike	$\tau_{INACT} > \tau_{DEINACT}$	frequency, time	0.1-1s	phasic	tonic + phasic hyper.	Ks	FF recurrent	Cx, Str, Hippoc.
Ramping	$\tau_{INACT} > \tau_{DEINACT}$	frequency	s	phasic	tonic + phasic hyper.	Ks	recurrent	Cx
Finite plateau	fold bifurc. vicinity	frequency, time	0.1-1s	phasic	tonic	Ca, Ksub	OCL	Cb
Finite valley	fold bifurc. vicinity	frequency, time	0.1-1s	phasic	tonic	Ca, Ksub	OCL	Cb
Infinite plat. and valleys	bistability	frequency	s	phasic	tonic	Ca, Ksub	OCL	Cb

Table 1. Comparative summary of the different cellular short-term memory properties previously discussed. Binary code means absence or presence of the OFF transition. Phasic: transient synaptic barrage; tonic: sustained synaptic barrage. FF: feed-forward; OCL: Olivo-cerebellar loop. Cx: neocortex; SC: spinal chord; Str: striatum; Hippoc: hippocampus; Cb: cerebellum.

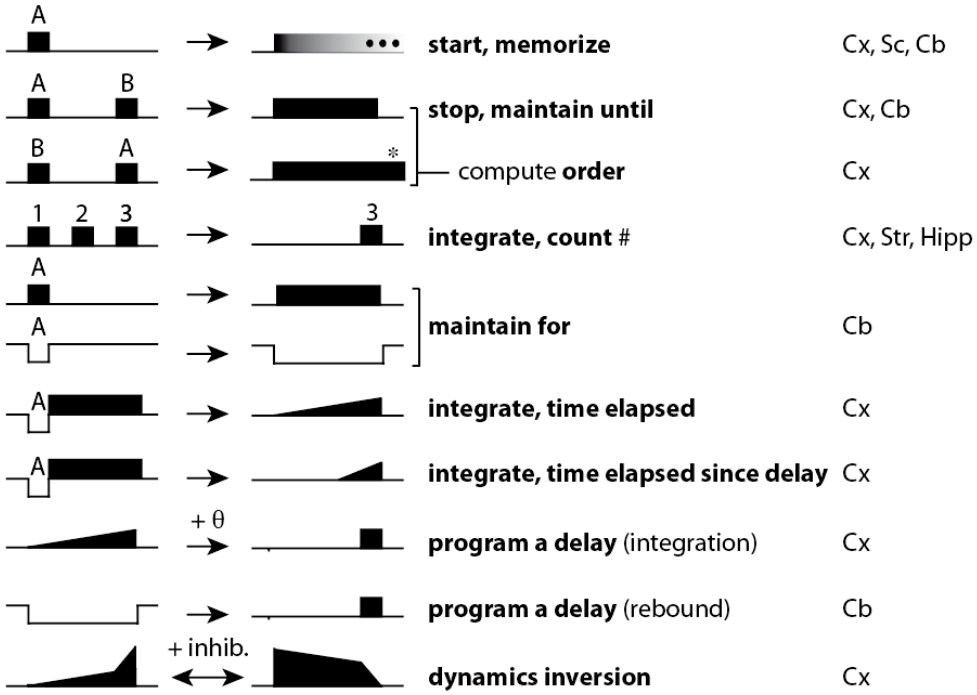

Fig. 16. Temporal computations from cellular short-term memory properties. Black areas amplitude represents firing frequency. Negative steps represent periods of hyperpolarization. θ : threshold. In the example of order computation, one considers $\theta_{ON} < A < \theta_{OFF} < B$. Cx: neocortex; Cb: cerebellum; Str: striatum; Hipp: hippocampus.

Moreover, considered alone, or combined with a few other ubiquitous electrophysiological features, they represent biophysical implementation of *temporal operations* (Fig. 16). Indeed, self-sustained discharges arising from cellular bistability or multistability and triggered by ON transitions can *memorize* or *maintain* past stimuli. Combined together, ON and OFF transitions implement a *maintain until* operation. Complementary, the finite plateaus and valleys of PCs implement a form of maintenance where duration is determined prior to the period of maintenance, i.e. a *maintain for* (a given time) operation. The initiation and termination of self-sustained activities can also simply be interpreted as *start* and *stop* operations with regard to a downstream program of activity to be engaged (e.g., a pattern generator, or another program or sequence). Given a few conditions on the thresholds for ON and OFF transitions and input amplitudes, the *order* of two successive inputs can be computed explicitly and maintained for future computations (e.g. sequence recognition) under the form of a sustained activity itself. The facilitation of successive inputs provided by Ks conductance (memory of excitation) is a form of *integration* of phasic inputs that can *count* whether a given number of inputs is reached (depending on the basal level of polarization and the duration and magnitude of inputs). The memory of inhibition of Ks conductance also performs integration (of tonic inputs) and yields the ability to produce a *delay* (first-spike-latency) and represent the *time elapsed* since a phasic input (ramp). Ramping activity, combined to the threshold of a downstream unit, or a PC valley combined with a rebound property also allow programming a *delay*. Finally, inhibition, combined, e.g. with a ramp yields the possibility for *dynamics inversion*, i.e. the ability to represent the mirrored trend of a neuronal activity. Thus, intrinsic properties of central neurons provide an extremely rich repertoire of temporal operations. These properties may in principle take an essential part in setting the dynamics of a large set of higher order cognitive processes such as decision-making [118], retrospective and prospective memory [93], scalar timing [119], counting [120], or order detection [121].

Remarkably, it has been recently noticed that the question of whether intrinsic properties may play a significant role in essential properties of long-lasting firing patterns in recurrent neural networks has remained largely unexplored [96,111]. This is quite ironical since the “intrinsic hypothesis” has been customary considered as the traditional alternative hypothesis to the synaptic theory of persistent activity maintenance, which has been extensively assessed. Indeed, biophysically realistic models addressing the role of intrinsic conductance are absolutely scarce. The combined dopamine modulation of several intrinsic (NaP, Ks, high-threshold Ca) conductance together with that of AMPA, NMDA and $GABA_A$

synaptic conductance was shown to increase the stability of persistent activities to distractors in a recurrent network model of the prefrontal cortex [122]. In another recurrent network model, it was demonstrated that calcium-activated cationic (CAN) conductance reduce the requirement for the proportion of NMDA-mediated excitatory synaptic transmission for network stability [123]. The last contribution is our study of the possible role of the Ks conductance to ramping activities (Part 4; [37]). Other studies have focused on the possible role of cellular bistability in the maintenance of graded persistent activity but they rely on rate descriptions of neuronal activity and do not evaluate the effective contribution of intrinsic conductance to long-lasting activities [105,107].

Therefore, to our knowledge, there has been no systematic attempt yet to evaluate the possible contribution of intrinsic properties in the existence of long-lasting activities at the network level. In the following, we assess an *intrinsic hypothesis for persistent activities*, i.e. the possibility that intrinsic conductance take an essential part in persistent activities in recurrent neural networks, which dynamical and statistical properties are currently not accounted for satisfactorily by theories based purely on synaptic reverberation. As a essential correlate of the intrinsic hypothesis we formulate, intrinsic plasticity, the plasticity of intrinsic properties, would represent a powerful plastic mechanism accounting for the set-up, adaptation or extinction of persistent activities observed in behavioral conditions.

Indeed, strong evidence indicates that neurons ubiquitously undergo anti-homeostatic instrinsic plasticity (IP/AH; [18,73,124,125,126,127,128]), in which neuronal activity and the regulatory state of conductance form a positive loop. Such loops typically display bi- or multi-stability that are largely recognized as central dynamical mechanisms underlying plasticity and memory [52]. Thus, IP/AH is likely providing a mechanism for information storage that could complement Hebbian learning [127]. Indeed, IP/AH has recurrently been demonstrated as a cellular correlate of classical and operant conditioning, and of rule learning in invertebrates and vertebrates neurons (e.g. [129]). Moreover, evidence indicates that IP/AH induction operates at the time scale of seconds, by contrast to homeostatic IP (IP/H), which develops over hours or days [128]. Therefore, IP/AH possess logical and time-scale properties ideally suited to engage the set-up, adaptation or extinction of persistent activities. For instance, the repetition of external phasic feed-forward inputs to the network may trigger activity-dependent IP/AH, increasing the excitability of stimulated neurons, eventually leading to the set up long-lasting activities in the network. Thus, IP/AH could play a preeminent role in the setup of behaviorally relevant neuronal dynamics through on-going, activity-dependent modifications of the computational properties of neurons (e.g. firing level

or pattern, information processing capabilities). Whereas this possibility radically challenges the classical conception of neurons embedded with a fixed dynamical regime of operation, no realistic model of the effect of IP/AH in recurrent neural networks exists currently to our knowledge.

7. Specific goals

The specific addressable questions we intend to assess are the following.

- Is a reliable form of parametric working memory achievable in a recurrent neural network with unstructured synaptic connectivity, when neurons are endowed with a realistic description of intrinsic conductance?
- Would such a model ensure statistics compatible with those observed experimentally for parametric working memory, i.e. higher coefficients of variation during persistent activity and typically >1 ?
- Would intrinsic plasticity allow the set-up, adaptation and extinction of persistent activity within a few trials upon contingencies changes, as observed empirically?

8. Methods

These questions will be assessed through simulations and analysis of spiking recurrent neural network models. The network architecture will follow canonical cortical connectivity statistics: 80% of excitatory neurons, inhibition of inhibition, balanced excitatory and inhibitory synaptic transmission, sparseness with probability of connection between two neurons 0.15, and random excitatory and inhibitory synaptic weights (unstructured network). For computational reasons, neurons will at first be described as integrate and fire units endowed with a fine-grained description of their intrinsic conductance, i.e. leak and voltage- and/or calcium-dependent conductances. Our recent study of IP effects has allowed us providing an analytical simplified but accurate description of conductance activation/inactivation dynamics during the spike in integrate and fire neurons (Naudé et al., *in revision*). In doing so, it is possible avoiding the typical larger computation times of Hodgkin-Huxley simulations while keeping a precise estimate of gating variable dynamics, which are essential to the network dynamics. The rules for intrinsic plasticity will be based on aKP cycle dynamics [8].

9. Preliminary results and first perspectives

To assess the feasibility and pertinence of the intrinsic hypothesis, we have simulated such a network of 300 neurons. In a subset (half) of excitatory neurons (X neurons), we have considered the presence of an intrinsic inward conductance (g_X) with activation but no inactivation. Otherwise, neurons comprised a single leak conductance. This distribution of conductance in the network was considered as the outcome of previous anti-homeostatic intrinsic plasticity due to repeated excitation of X neurons by past sensory inputs (e.g.). Stimulating X neurons for $100ms$ at $t = 900ms$ triggered a persistent firing in these neurons (Fig. 17A). This long-lasting activity typically lasted several seconds and eventually drifted back to baseline spontaneous spiking, often in a non-monotonous fashion. During a 1s delay, firing frequency was stable in the population of X neurons (Fig. 17B, orange trace). Moreover, this maintenance was selective because 1) other excitatory neurons and inhibitory neurons rested a spontaneous level of discharge during persistent activity in X neurons (Fig. 17A), 2) triggering firing in other excitatory neurons did not induce persistent activity (Fig. 17C, yellow trace). Moreover, the level of persistent activity increased with that of the triggering stimulus (Fig. 17D) and the mean firing frequency was a slightly supra-linear function of the stimulus, as observed empirically (Fig. 17E; [41]). Furthermore, we found that the coefficient of variation of the firing was superior during the delay, compared to in the spontaneous state and superior to 1 during the delay, as found in behavioral conditions [109,111]. Moreover, we have found that these results were robust to 15% variations in the maximal conductance of the intrinsic conductance.

These results are extremely encouraging, since they demonstrate that parametric retrospective persistent activities can be achieved in recurrent neural network models endowed with realistic intrinsic properties in the absence of any fine-tuning or specific symmetry of the synaptic matrix, as the network is unstructured (random) in our case. Moreover, the currently yet unexplained statistics of delay activity observed experimentally appear as a natural property when intrinsic properties are taken into account. Obviously, these preliminary results must be extended. Among other questions, a systematic analysis of the conductance and network parameters required to produce parametric retrospective persistent activities appears as a first step to delineate the mechanism at work here. Of cardinal importance, another perspective is to provide a theoretical account of the underlying mechanisms through mean-field analysis. In particular to determine to which extent the intrinsic properties of X neurons and synaptic recurrence take part to persistency. Moreover, it

is also essential to determine whether coupling X conductance with a realistic model of IP/AH derived from aKP cycles will allow gaining fast plasticity and extinction of this parametric retrospective persistent activities, as observed experimentally. Incidentally, it would also be very interesting to determine how these persistent activities are compatible with different scenarios of OFF transitions and whether they allow the co-existence in the same network of ramping activities, possibly with the introduction of slowly-inactivating conductance.

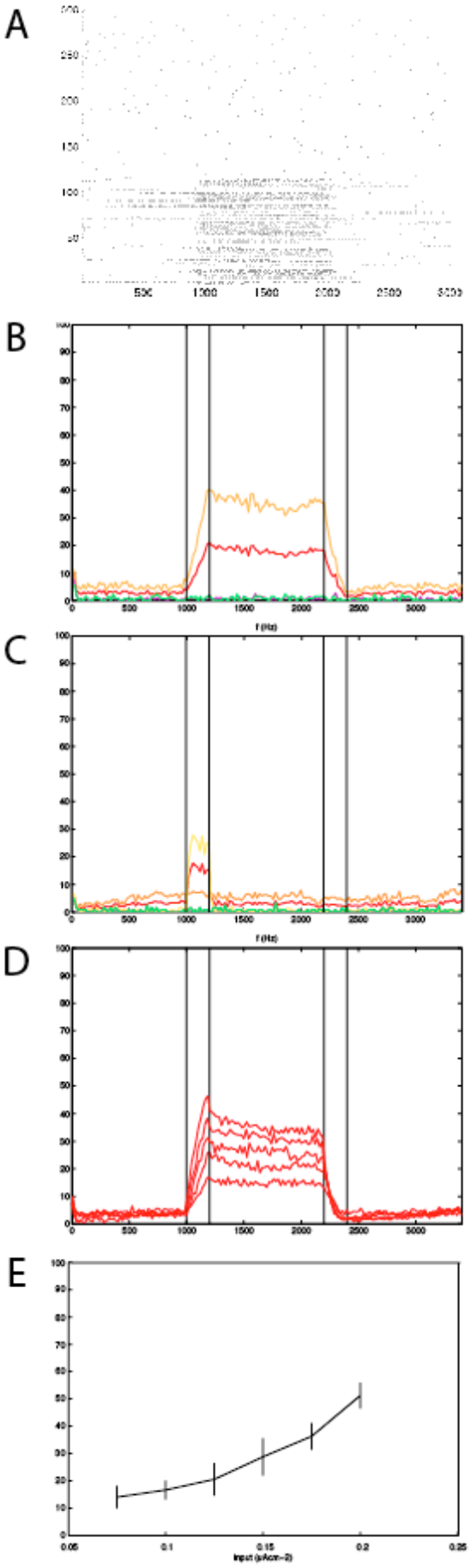

Fig. 17. A. Raster plot of the 300 neurons of the recurrent network. Neurons 1-240 are excitatory. Neurons 1-120 are endowed with an inward conductance and stimulated with $I = 0.1 mScm^{-2}$ for $100ms$ at $t = 900ms$. **B.** Firing frequency of neurons endowed with the intrinsic conductance (orange trace) and of all excitatory neurons (red trace). **C.** Similar to B., except that the excitatory neurons stimulated are those with no intrinsic conductance (yellow trace) are with $I = 0.5 mScm^{-2}$. **D.** Firing frequency of all excitatory neurons with increasing values of the input current. **E.** Mean firing frequency during the delay period as a function of the input current.

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