A cellular mechanism makes switches in brain states compatible with synaptic plasticity

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Summary
Animal performance relies on their ability to quickly process, analyze and react to incoming events, as well as to learn from experience to constantly increase their knowledge about the environment. Learning and memory are attributed to the ability of neurons to modify their connections with other cells based on experience, a property called synaptic plasticity. Synaptic plasticity mechanisms often exploit the level of correlation in the activity of connected neurons, and can therefore be affected by abrupt changes in neuronal excitability. On the other hand, brain information processing is constantly shaped by fluctuations in neuronal rhythmic activities at the cellular and population levels, each defining distinctive brain states. Switches between these brain states can be fast and localized, such as e.g. those observed in different brain areas prior to movement initiation, or global and long lasting, such as those observed during the wake-sleep transition. The coexistence of these two mechanisms raises challenging questions: how can switches in brain states remain reliable despite of constant rewiring of neuron connectivity, and how is synaptic plasticity affected by switches in brain states? In this work, we highlight the critical role of a cellular dynamical property in the generation of switches in brain states that are compatible with changes in network connectivity and cellular heterogeneity. This dynamical property, called slow regenerativity, is accessible to all neurons that embed slowly activating voltage-gated calcium channels or slowly inactivating potassium channels in their membrane, yet it is largely overlooked in computational and mathematical neuron models and absent from all available hybrid models. To demonstrate this point, we compare the robustness of 5 published thalamic neuron models at the cellular, circuit and population levels. We show that the robustness of rhythms at the population level correlates with the presence or absence of slow regenerativity at the cellular level.

Central question and research approach
The present work focuses on one central question: how can switches in brain states, which play an important role in brain information processing, be compatible with synaptic plasticity, the central mechanism of learning and memory? Indeed, little is known about how shifts in network rhythms such as those observed during sleep influence synaptic plasticity, hence learning. One reason for this puzzle is that state-of-the-art computational models of switches in brain states have often focused on the role of connectivity changes in network rhythm modulation. Such models are not appropriate to study the impact of transient network oscillations on synaptic plasticity and learning, since the rhythmic switch itself relies on a disruption of the connectivity established through learning. Here, we highlight the role of slow regenerativity, a cellular property, in generating network transitions that are robust to variability and heterogeneity at the cellular and network levels, making the switching mechanism largely independent from network topology, and therefore compatible with synaptic plasticity. First, we show that this cellular property is often barely present or even absent in state-of-the-art conductance-based models and hybrid models, and that this absence correlates with a lack of robustness in the network rhythm. Second, we show that slow regenerativity can be embedded in simple hybrid neuron models without increasing the complexity of the model. This opens the possibility to study the interactions between switches in network rhythmic activity and synaptic plasticity in large neuronal populations.

Methods and results

We compare the robustness of four well-established conductance-based models of thalamic neurons composed of a similar number of ionic currents (Wang, 1994; Rush and Rinzel, 1994; Desthexe et al., 1998; Drion et al., 2018). Each of these models is capable of reproducing the different firing patterns observed in thalamic neuron (a depolarized tonic mode, a hyperpolarized bursting mode, rebound bursting, etc.) and the switch between them. However, two of these models incorporate the role of slow regenerativity (Desthexe et al., 1998; Drion et al., 2018), and two others do not (Wang, 1994; Rush and Rinzel, 1994). This comes from the fact that the two latter models neglect the activation dynamics of T-type calcium channel by modeling the activation as an instantaneous event, a simplification often encountered in neuronal modeling. In addition, we restore slow regenerativity in the model of (Rush and Rinzel, 1994) by adding slow dynamics for T-type calcium channel activation, making the analysis of the role of slow regenerativity as fair as possible.

We create excitatory-inhibitory networks of variable size using the four different neuron models described above. Neurons are connected through AMPA, $GABA_A$ and $GABA_B$ connections to model the asymmetric coupling between a subpopulation of excitatory (E) cells and a subpopulation of inhibitory (I) cells. We start with an isolated E- I circuit of two cells in configurations where all neuron models are capable of generating switches in network rhythm. We then study the robustness of these network switches to changes in neuron intrinsic properties (maximal conductances), mimicking the effect of neuromodulation, and changes in synaptic weights, mimicking the effect of synaptic plasticity. One hundred 2-cell networks were simulated for each model by generating different parameter sets for maximal intrinsic conductances and synaptic weights. The percentage of rhythmic networks that have performed the rhythmic transition is evaluated for an increasing variability in each conductance-based model. Networks composed of models incorporating slow regenerativity are more robust than those from which this cellular property is absent, and restoring slow regenerativity in one model significantly increased the robustness of the switch (Fig. 1A). We then reproduce this experiment for larger neuronal populations (200 cells). In bigger networks, switches in the mean-field rhythmic activity are illustrated in the local field potential (LFP) activity. Again, network rhythms generated by models that incorporate slow regenerativity are robust against network heterogeneity, whereas these rhythms are fragile in the absence of this cellular property (Fig. 1B).

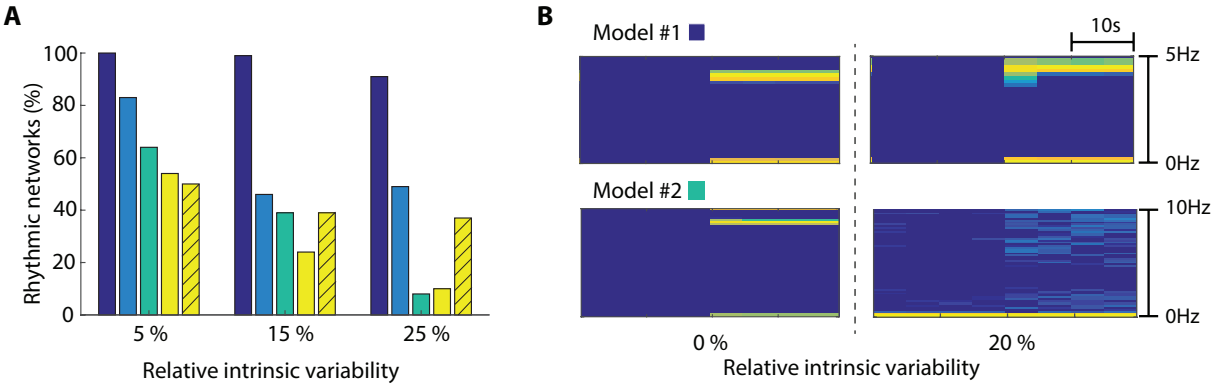

Figure 1 – A. Proportion of rhythmic network activities observed in different neuron models as intrinsic variability increases. Dark blue: Drion et al., 2018; light blue: Destexhe et al., 1998; green: Wang, 1994; yellow: Rush and Rinzel, 1994; yellow hatched: Rush and Rinzel, 1994 with slow T-type calcium channel activation. **B.** Spectogram of LFP activity of neuronal populations made of two different neuron models (top: Drion et al., 2018; bottom: Wang, 1994) without heterogeneity (left) and with 20% of intrinsic heterogeneity (right). The appearance of a yellow line in the spectrogram represents a switch in population rhythm.