Sleep Oscillations

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Introduction

The brain spontaneously generates complex patterns of neural activity. As the brain falls asleep, the rapid patterns characteristic of aroused states are replaced by low-frequency, synchronized rhythms of neuronal activity. At the same time, electroencephalographic (EEG) recordings shift from low-amplitude, high-frequency rhythms to large-amplitude, slow oscillations. In what follows, we focus primarily on this slow-wave sleep, rather than rapid eye movement (REM) sleep, whose oscillatory properties resemble those of wakefulness.

The thalamus and cerebral cortex are intimately linked by means of reciprocal projections. The thalamus is the major gateway for the flow of information toward the cerebral cortex and is the first station at which incoming signals can be blocked by synaptic inhibition during sleep. This shift contributes to the transition that the brain undergoes from an aroused state, open to influence from the outside world, to the closed state of sleep. The early stage of

quiescent sleep is associated with EEG spindle waves, which occur at a frequency of 7–14 Hz. As sleep deepens, waves with slower frequencies (0.1–4 Hz) appear on the EEG. This article summarizes what is known about the biophysical mechanisms underlying spindle oscillations.

The dramatic reduction in forebrain responsiveness during sleep, the pervasiveness of these changes, and the discovery of the underlying specific cellular mechanisms, suggest that sleep oscillations are highly orchestrated and highly regulated. Experimental and modeling studies have shown how sleep rhythms emerge from an interaction between the intrinsic firing properties of thalamic and cortical neurons and the networks through which they interact (Steriade, McCormick, and Sejnowski, 1993; Destexhe and Sejnowski, 2001). These advances have raised interesting possibilities regarding the function of sleep.

Biophysical Basis of Sleep Spindle Oscillations

Sleep spindles are characteristic of brain electrical synchronization at sleep onset, an electrographic landmark for the transition from waking to sleep that is associated with loss of perceptual awareness. Spindle oscillations consist of 7–14 Hz waxing-and-waning field potentials, grouped in sequences that last for 1–3 s and recur once every 3–10 s. Spindle oscillations constitute an interesting and well-constrained problem to investigate by computational models for several reasons. First, these oscillations are generated in the thalamus, which is a well-known structure anatomically, with well-defined connectivity between the different cell types. Second, spindles are remarkably well documented experimentally and have been extensively characterized both in vivo and in vitro (reviewed in Steriade et al., 1993; Destexhe and Sejnowski, 2001). Third, this oscillation is generated by an interplay of complex cellular properties, such as burst firing, and synaptic interactions via multiple types of postsynaptic receptors (reviewed in Destexhe and Sejnowski, 2001). Computational models are needed to understand this complex interplay, as we summarize here.

The typical electrophysiological features of spindle oscillations are shown in Figure 1*A*. The two cell types involved, thalamocortical (TC) and thalamic reticular (RE) neurons, oscillate synchronously and display burst discharges according to a mirror

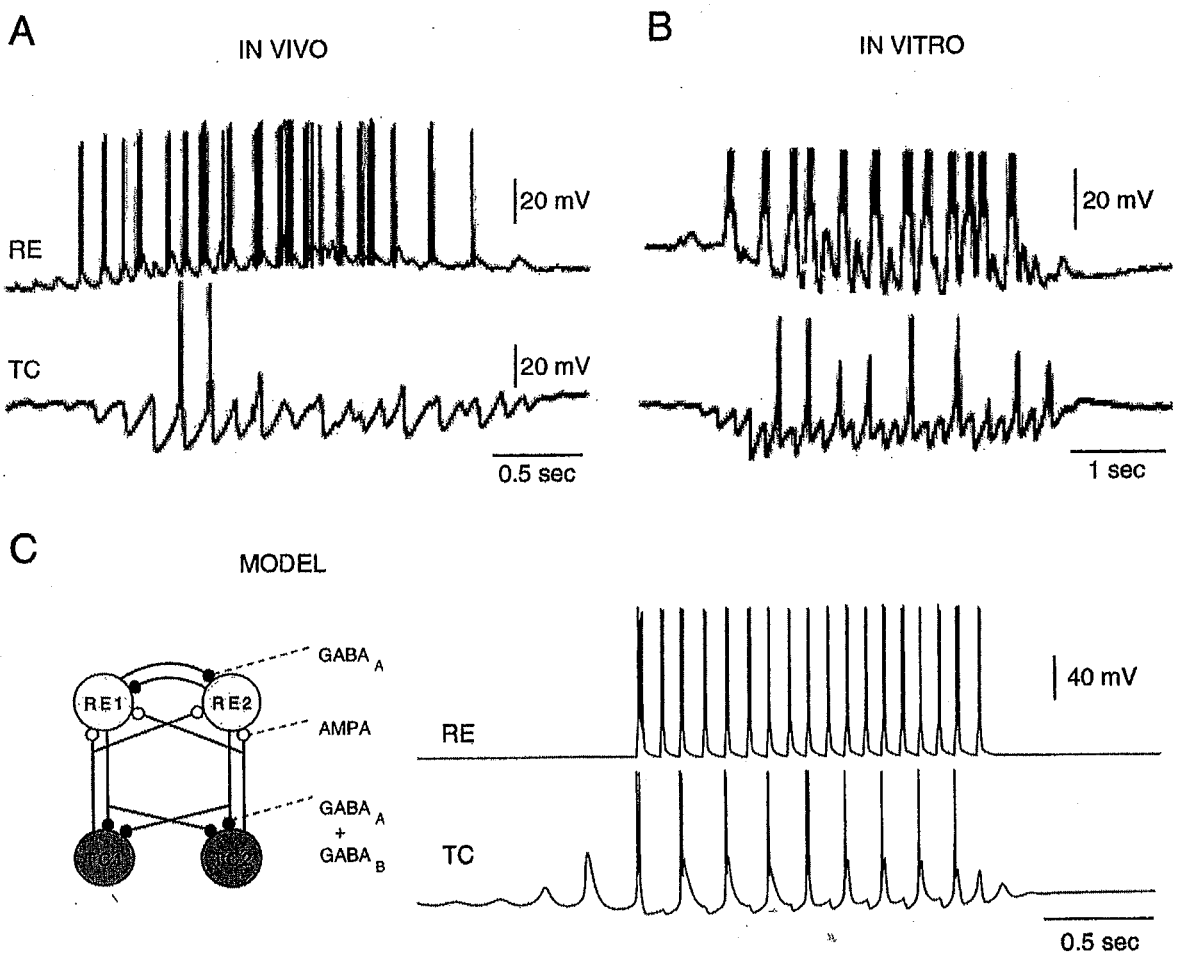

Figure 1. Spindle oscillations in thalamic circuits. *A*, Intracellular recordings of thalamic neurons during spindle oscillations in vivo (cats, barbiturate anesthesia; modified from Steriade et al., 1993). *B*, Intracellular features of spindle oscillations in ferret thalamic slices (spikes truncated; modified from Steriade et al., 1993). *C*, Model of spindle oscillations by interacting TC and RE cells. The intrinsic firing properties of each cell type was simulated by Hodgkin-Huxley type models for Na^+, K^+ and Ca^{2+} currents, and kinetic models of postsynaptic receptors (AMPA, $GABA_A$, and $GABA_B$; see scheme) were used to represent synaptic interactions (modified from Destexhe et al., 1996; see also Destexhe, Mainen, and Sejnowski, this volume). In all three examples, RE cells generated bursts following EPSPs while TC cells generated bursts following IPSPs once every few cycles.

image: RE cells display bursts following excitatory synaptic potentials (EPSPs) while TC cells burst following inhibitory postsynaptic potentials (IPSPs). Although RE cells tend to burst at every cycle of the oscillation, TC cells only produce bursts once every few cycles. These features are typical of spindles recorded in thalamic neurons in different mammals.

Several hypotheses for the genesis of oscillations by thalamic circuits have been proposed (reviewed in Destexhe and Sejnowski, 2001). These involve reciprocal synaptic interactions between TC neurons and local inhibitory interneurons, loops between TC and RE neurons, or loops within the RE nucleus. The involvement of the RE nucleus was firmly demonstrated in a series of experiments by Steriade's group (reviewed in Steriade et al., 1993; Destexhe and Sejnowski, 2001). In particular, the deafferented RE nucleus in vivo can exhibit spindle rhythmicity in extracellular recordings. In contrast, the RE nucleus does not display autonomous oscillations in vitro, but spindles have been observed in thalamic slices based on TC-RE interactions (see Steriade et al., 1993, for a review of these issues). These in vitro spindles display the same intracellular features as in vivo (Figure 1*B*).

The genesis of spindle oscillations was investigated with computational models. First, in models of the isolated RE nucleus, RE neurons with sufficiently high connectivity interacting through GABAergic synapses generated spindle rhythmicity (Wang and Rinzel, 1993; Destexhe et al., 1994; Bazhenov et al., 1999; reviewed in Destexhe and Sejnowski, 2001). These models supported the RE pacemaker hypothesis based on in vivo recordings. Second, models including TC and RE cells showed that spindle oscillations can be obtained from TC-RE loops (Destexhe et al., 1996; Golomb, Wang, and Rinzel, 1996). The latter models supported the TC-RE mechanism suggested by thalamic slice experiments. Finally, it remained to explain why the RE nucleus oscillates autonomously in vivo but not in vitro. This apparent inconsistency was addressed by a computational model of the RE nucleus, in which oscillations depended on the level of neuromodulators (Destexhe et al., 1994). The difference between in vivo and in vitro preparations may therefore be explained by the limited connectivity between the RE neurons in the slice, and/or by the fact that slices lack the necessary level of neuromodulation to maintain isolated RE oscillations (Destexhe et al., 1994). The main prediction from this model is that applying neuromodulators to slices of the RE nucleus should induce oscillations similar to those observed in vivo.

The model for the TC-RE loop is shown in Figure 1*C*. Neurons were modeled using Hodgkin-Huxley type representations of Na^+, K^+, and Ca^{2+} voltage-dependent currents (see AXONAL MODELING), which were based on voltage-clamp data on thalamic neurons (see details in Destexhe et al., 1996). These models reproduced the most salient intrinsic properties of thalamic neurons, such as the production of bursts of action potentials. Synaptic interactions were modeled using conductance-based kinetic models (see Destexhe, Mainen, and Sejnowski, this volume). Several of the main receptor types (AMPA, NMDA, $GABA_A$, and $GABA_B$) identified in thalamic circuits were incorporated into the model. Under these conditions, the circuit generated 7–14-Hz spindle oscillations with the typical features identified intracellularly in the different thalamic neuron types. The model reproduced the typical mirror image between TC and RE cells during spindles, as well as the phase relations between cells. In particular, TC cells produced bursts once every two cycles, a feature consistently observed experimentally (compare with Figure 1*A–B*). More irregular behavior, similar to the experiments, was obtained in larger networks or in the presence of the cortex (see the following discussion). The oscillations also showed the typical waxing-and-waning envelope of spindles; this property was due in the model to Ca^{2+}-mediated slow regulation of the I_h current, a prediction that was verified experimentally (Lüthi and McCormick, 1998).

Network Properties of Spindle Oscillations

Network properties were investigated using multiple recordings in vivo (Contreras et al., 1996) and in vitro (Kim, Bal, and McCormick, 1995). Spindle oscillations in vitro showed traveling wave patterns (Figure 2*A*). The oscillation started on one side of the slice and propagated to the other side, at a constant propagation velocity. Traveling spindle waves were simulated by computational models of networks of interconnected TC and RE cells (one-dimensional extensions of the circuit shown in Figure 1*C*), in two independent modeling studies (Destexhe et al., 1996; Golomb et al., 1996). These models were similar in spirit to the circuit shown in Figure 1*C*, but assumed that there was a topographic connectivity between TC and RE layers, consistent with anatomical data. Under these conditions, the models generated traveling waves consistent with in vitro data (Figure 2*B*).

In contrast to the thalamic slice, in recordings from the intact thalamocortical system in cats in vivo, the oscillations were remarkably synchronized over extended thalamic regions and showed little signs for traveling wave activity (Figure 2*C*). To simulate the in vivo conditions, a thalamocortical network model was developed by combining the previous model of thalamic slices with a model of deep cortical layers (see details in Destexhe, Contreras, and Steriade, 1998). The principal prediction of this model was that, in order to generate large-scale coherent oscillations, the cortex had to recruit the thalamus primarily through the RE nucleus. Because of the powerful inhibitory action of RE cells, the action of corticothalamic feedback is "inhibitory dominant" on TC cells, which property is essential to maintain large-scale synchrony (Destexhe et al., 1998). In these conditions, the same model was capable of generating large-scale synchrony in the presence of the cortex, and traveling waves in the isolated thalamus (Figure 2*D*). Consistent with these models, propagating activity has indeed been observed in the thalamus of decorticated cats in vivo (Contreras et al., 1996).

The cortical control of thalamic relay cells in the model through dominant inhibitory mechanisms has important consequences for the function of thalamocortical assemblies (see details in Destexhe and Sejnowski, 2001) and pathological situations such as absence seizures (Destexhe, 1998). As a result of inhibitory dominance, a too strong feedback can activate $GABA_B$ receptors and can entrain the *physiologically intact* thalamus into hypersynchronous rhythms at ~3 Hz. This scheme may explain the genesis of absence seizures, which are hypersynchronous ~3 Hz rhythms that appear suddenly in the thalamocortical system. These seizures can be provoked experimentally by altering the cortex, but a physiologically intact thalamus is required (Gloor and Fariello, 1988). The thalamocortical model accounts for these experiments and could simulate seizures based on inhibitory-dominant corticothalamic feedback (Destexhe, 1998). This model directly predicted that manipulating corticothalamic feedback should entrain the physiologically intact thalamus to generate hypersynchronous rhythms at ~3 Hz, a prediction that has been recently verified by two independent studies (Blumenfeld and McCormick, 2000; Bal, Debay, and Destexhe, 2000).

Finally, computational models have suggested a physiological role for spindle oscillations. The synchronized high-frequency bursts of action potentials in the thalamus provide a powerful input to the cortex, which is ideal for evoking massive calcium entry into pyramidal cells. Massive calcium entry may activate a series of biochemical cascades, leading to permanent changes of previously tagged synapses (Destexhe and Sejnowski, 2001). This scenario provides a biophysical mechanism consistent with the growing evidence that sleep serves to consolidate memories (see Destexhe and Sejnowski, 2001, for further details).

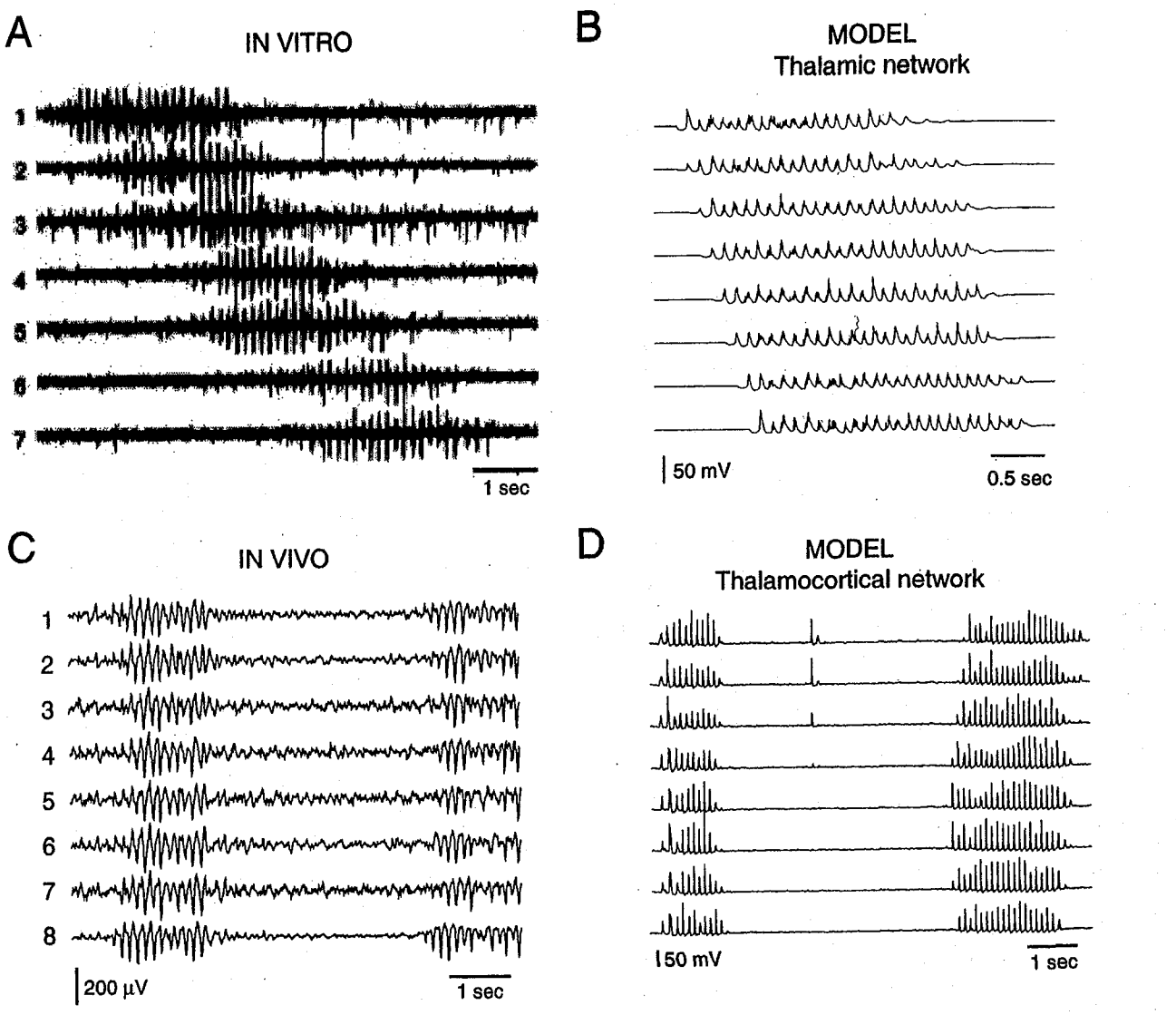

Figure 2. Sleep spindles in thalamic and thalamocortical networks. *A*, Propagating spindles in vitro. Spindle oscillations in an array of seven extracellular electrodes aligned along the dorsoventral axis of the slice (electrodes were separated by 250–400 μm, extending over 2–3 mm in the slice; modified from Kim et al., 1995). *B*, Propagating oscillations in a model thalamic network with reciprocal and topographic connections between TC and RE layers (100 cells total; modified from Destexhe et al., 1996). Each trace shows the averaged membrane potential (computed from ten neighboring TC cells) taken at eight equally spaced sites in the network. *C*, Large-scale synchrony of spindles in vivo. Eight extracellular electrodes were inserted along the dorsoventral axis of the thalamus in cats under barbiturate anesthesia (interelectrode distance of 1 mm; modified from Contreras et al., 1996). *D*, Large-scale synchrony in a thalamocortical network model consisting of four layers of thalamic and cortical neurons interconnected in a topographic fashion (400 cells total; averaged membrane potentials shown at ten equidistant locations; modified from Destexhe et al., 1998). While the oscillation was generated in the thalamus (see Figure 1), the large-scale synchrony depended on the cortex and was generated by corticothalamic interactions (see text for details).

We have shown here that computational models can simulate a large body of experimental data, ranging from isolated thalamic circuits to large-scale thalamocortical assemblies, also including the genesis of pathological behavior such as seizures. The challenge for future studies will be to investigate the physiological role of these slow-wave oscillations. Our present working hypothesis is that the high level of synchrony of these oscillations is ideal to recruit specific calcium-dependent biochemical cascades leading to memory consolidation, which may be one of the principal roles of sleep.

Summary and Conclusions

Computational models of neurons using conductance-based mechanisms integrate electrophysiological data from both in vitro and in vivo preparations. This approach reconciles apparently conflicting experimental data and has generated experimental predictions (some of which have been tested and verified). In particular, a coherent framework has been proposed to explain the genesis of sleep spindles and pathological behavior, such as absence seizures, based on data from the level of ion channels to large-scale network in-

teractions. These data have led to plausible hypotheses for a role of sleep oscillations in memory consolidation (see details in Destexhe and Sejnowski, 2001).

All models shown here were simulated using NEURON (Hines and Carnevale, 1997). Computer generated movies and NEURON programs to simulate these models are available at http://cns.iaf.cnrs-gif.fr and http://www.cnl.salk.edu/~alain/ or upon request.

Road Map: Biological Networks
Related Reading: EEG and MEG Analysis; Hippocampal Rhythm Generation; Thalamus

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