In: A. A. Borbely, O. Hayaishi, T. J. Sejnowski,
J. S. Altman (Eds.), The Regulation of Sleep,
Human Frontiers Science Program,
Strasbourg, 57-65 (1996).

Computational neurobiology of sleep rhythms

Terrence J. Sejnowski

Computational models are a useful way to step between the two levels of description reported in the preceding articles: the distribution and synchrony of the oscillatory activity occurring during non-REM sleep in vivo and the behaviour of the underlying ionic conductances in vitro (see Steriade, McCormick, this volume). Experimentally determined parameters, such as how

membrane potential and ionic currents change under different conditions can be incorporated into a number of model neurons connected in a manner that resembles the network in vivo. Such model networks can be used to test whether all the component currents and connections involved in generating the behaviour of the network have been accounted for. If not, adjustments can be made to the model that lead to predictions about the missing component(s), which can then be sought experimentally.

This iteration between experimental preparation and model has proved a powerful tool for deepening our understanding of how oscillations are generated in several neuronal systems (Ritz and Sejnowski, 1997). I review here computational models that evaluate specific hypotheses for the generation of spindle waves during the transition from the awake state to non-REM sleep and make predictions that can be experimentally tested (for review, see Destexhe and Sejnowski, 2000). At a further remove, the models also indicate a possible function for the oscillations during non-REM sleep in establishing long-term plastic changes in the network, a prediction that remains to be tested.

Models of thalamic spindle oscillations

The interplay between the intrinsic properties of thalamic reticular and thalamocortical neurons and their synaptic interactions responsible for the 6–15 Hz spindle waves has been revealed by intracellular recordings and computational modelling (*Figs 10, 15a*; Steriade *et al.*, 1993*c*; see McCormick, this volume). The first model of these interactions was a simple circuit representing a single thalamocortical neuron reciprocally interacting with one reticular neuron, which was sufficient to demonstrate the essential features of spindle waves (*Fig. 15b*; Destexhe *et al.*, 1993).

Network models incorporating more precise representations of the intrinsic and synaptic currents indicated that the waxing and waning of spindle waves results from an increase in the hyperpolarization-activated current, I_h (Destexhe *et al.*, 1996;

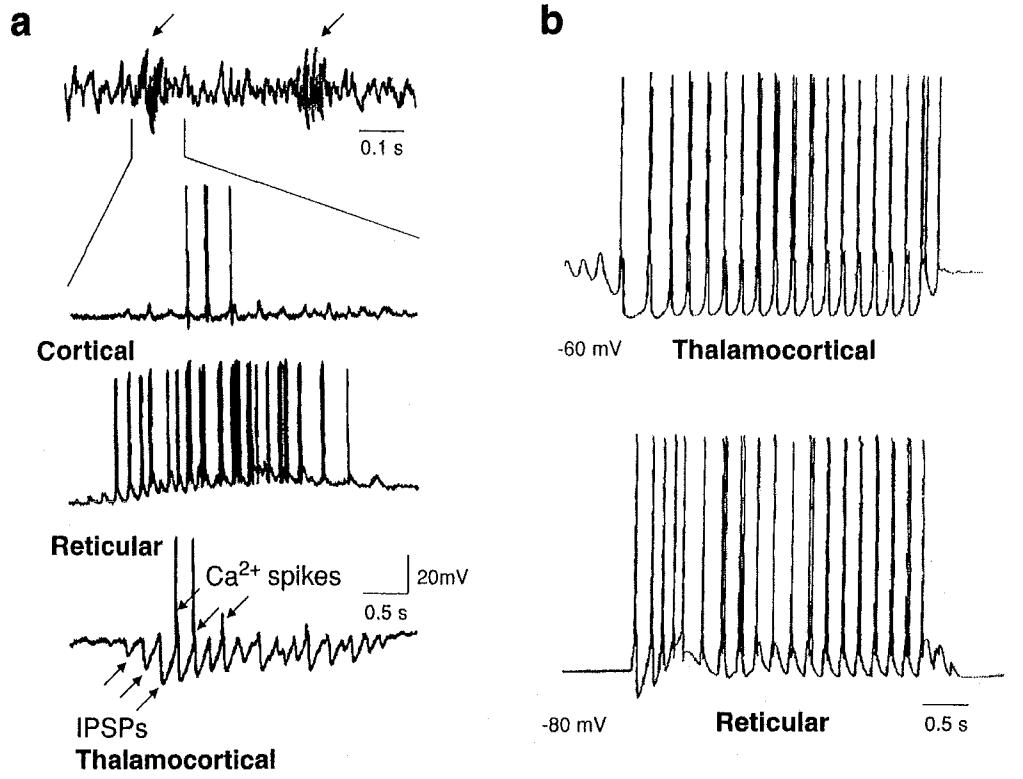

Figure 15. *Synaptic interactions that generate spindle waves in the thalamus during sleep.* ***a****, spindles recorded in vivo through a microelectrode inserted in intralaminar centrolateral thalamic nucleus of a cat with forebrain isolated by an upper brainstem transection. Top trace, two spindle sequences (arrows) with lower-frequency Δ waves between them. Lower traces, one spindle sequence recorded in cortical, thalamic reticular and thalamocortical neurons.* ***b****, computer model of 8–10 Hz spindle waves in a pair of interconnected thalamocortical and reticular neurons (Destexhe et al., 1993). A burst of spikes in the thalamocortical neuron excites the thalamic reticular neuron, which hyperpolarizes and produces a rebound burst in the thalamocortical neuron. The spindle wave is terminated by a shift in the voltage dependence of* I_h *as intracellular* Ca^{2+} *increases. Modified from Steriade* et al., *1993*c.

see McCormick, this volume). Recent experimental confirmation of this regulation in thalamic slices using caged Ca^{2+} has also shown that Ca^{2+} does not act directly on I_h ion channels but involves intermediate messengers (Luthi and McCormick, 1998; see McCormick, this volume). Another prediction was that I_h increases because the I_h channels are bound in the open state, which seems to be confirmed by recent experiments (see McCormick, this volume). The model thus drew attention to the

important consequences that changes in the properties of the I_h channel have for the thalamic network. As well as regulating the waxing and waning of spindles, they are also important during the refractory period between spindles, when the free Ca^{2+} returns to a lower concentration (Destexhe *et al.*, 1996).

Spindle oscillations in the thalamic reticular nucleus

Spindle waves in the thalamocortical network are abolished when the thalamic reticular nucleus is isolated from the rest of the thalamus and cerebral cortex; however, the deafferented reticular nucleus can still generate oscillations at spindle-wave frequencies (Steriade *et al.*, 1987). This endogenous oscillation may result from the interconnections between the neurons within the nucleus, through which they may couple and interact.

Modelling the generation of this endogenous rhythm illustrates well how models may not reach the right solution at first but still lead to experiments that point to the correct conclusion. The initial model, based on the intrinsic firing properties of the neurons and the GABA-mediated synapses between them, successfully reproduced the spindle rhythm produced by the isolated nucleus (Destexhe *et al.*, 1994). However, the proposed mechanism required mutual inhibitory-rebound interactions between the reticular neurons, which works only if the currents through the $GABA_A$-receptor linked channels are strong. Experimental observations did not confirm this (Ulrich and Huguenard, 1997).

We recently proposed an alternative mechanism based on the experimental observation that IPSPs are reversed in thalamic reticular neurons (Bazhenov *et al.*, 1999). When a neuron is strongly hyperpolarized, the chloride currents that generate the IPSP invert, producing a positive deflection in the recorded membrane potential, termed a reversed IPSP. Intracellular recordings in vivo show that, at the hyperpolarized membrane potentials that occur in thalamic reticular neurons during sleep,

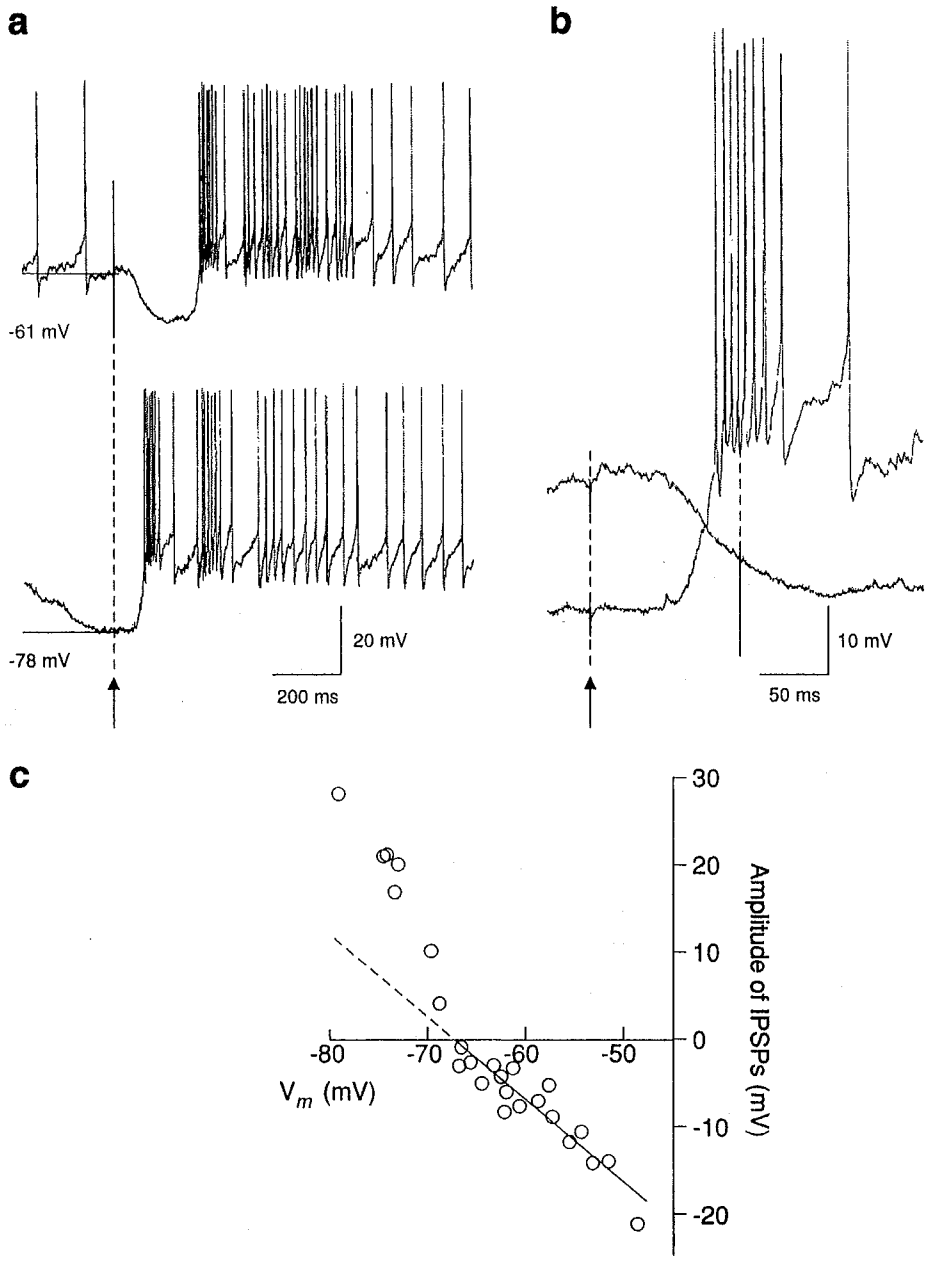

Figure 16. *Reversed IPSPs in a thalamic reticular neuron, in vivo with thalamocortical connections intact, trigger a low-threshold spike.* ***a***, *responses of a thalamic reticular neuron to a single stimulus in the thalamic VL nucleus (arrow). Top trace, when the neuron was relatively depolarized (-61 mV), a low-intensity stimulus evoked an IPSP-rebound sequence. Lower trace, when the same stimulus occurred at -78 mV during the hyperpolarizing phase of the slow oscillation, the IPSP reversed and, after 40–50 ms, triggered a low-threshold spike crowned by a burst of spikes.* ***b***, *the early part of the responses enlarged.* ***c***, *the amplitude of the postsynaptic response 75 ms after the stimulus plotted against the membrane potential (V_m). The amplitude of the IPSP depended linearly on V_m from depolarized levels to the reversal potential at -68 mV (solid line), when the IPSP activated the low-threshold spike, deflecting the function into depolarization (dotted line). Modified from Bazhenov* et al., *1999.*

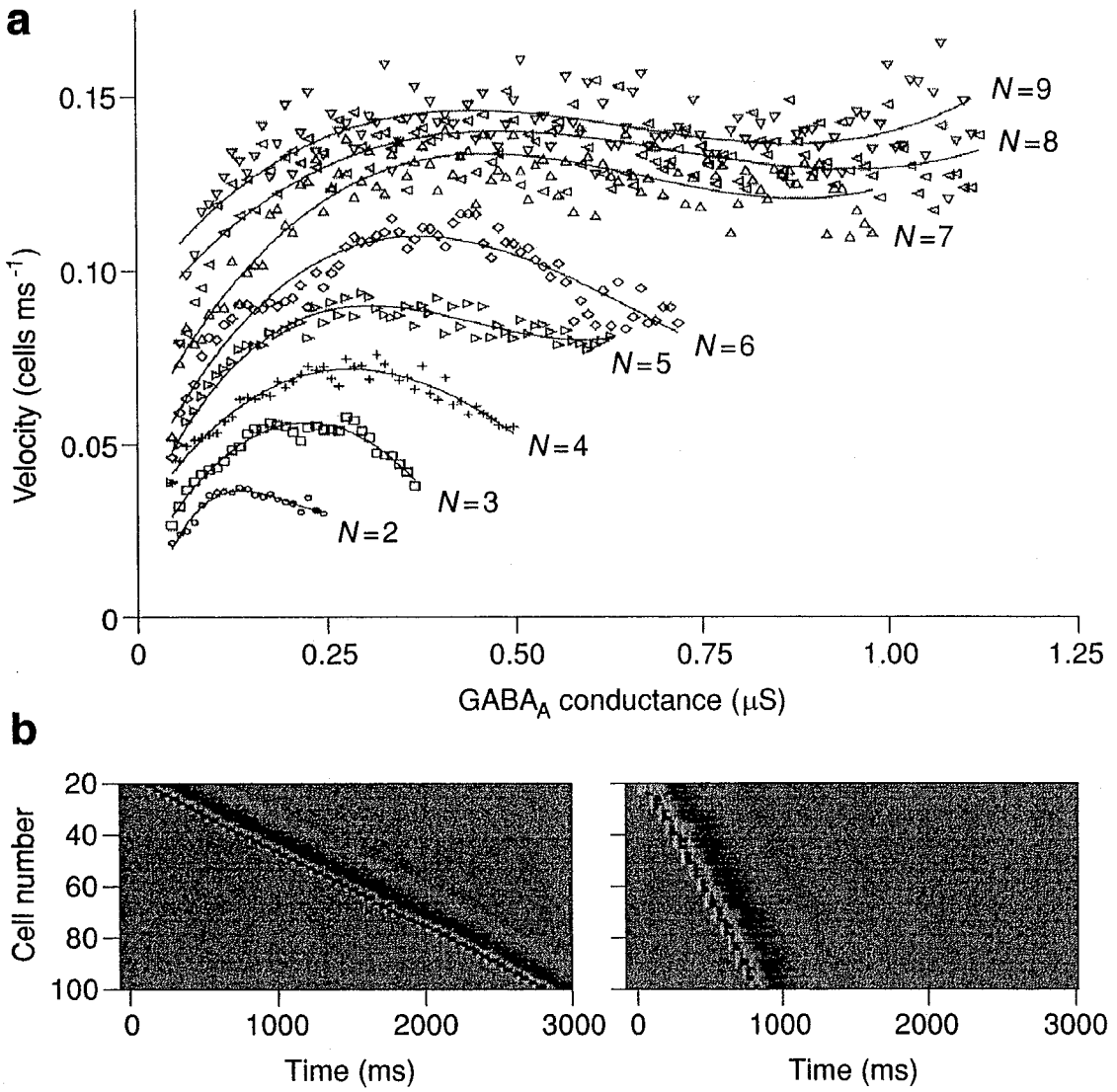

Figure 17. *Modelling the isolated thalamic reticular nucleus as a one-dimensional network in which reversed IPSPs trigger a low-threshold spike (see* Fig. 2*). The strength of depolarization through $GABA_A$-mediated synapses and the number of connections per neuron combine to produce a travelling wave of excitation through cells of the network.* ***a****, velocity of propagation of the travelling wave as a function of the conductance of the $GABA_A$-receptor linked channels. For connection radius (*N*) > 6 and $GABA_A$ conductance > 0.2 μS, the speed of propagation was only weakly dependent on these two parameters. Solid curves, nonlinear fits of the data.* ***b****, localized activity patterns propagating with different velocities. Left, $GABA_A$ conductance = 0.1 μS,* N = 2*; right, $GABA_A$ conductance = 0.4 μS,* N = 7*. Black areas represent depolarization. Modified from Bazhenov* et al.*, 1999.*

reversed IPSPs from other neurons in the nucleus can trigger a low-threshold spike (*Fig. 16*). Thalamic reticular neurons may thus interact through depolarization.

A network model in which reticular neurons interacted through reversed IPSPs generated sustained oscillatory behaviour (Bazhenov *et al.*, 1999). In a one-dimensional network, i.e., a chain of neurons, external stimulation evoked waves of excitation propagating at a velocity that ranged between 25 and 150 cells s^{-1} but that was constant for each strength of the inhibitory connections tested (*Fig. 17*). The waves of excitation required depolarizing GABA-mediated interactions but sustained oscillations were not generated. This correlates with the absence of oscillations in the isolated reticular nucleus in thalamic slices (von Krosigk *et al.*, 1993), which is mostly one dimensional.

Two-dimensional model networks, however, produce a regenerative oscillatory activity that forms rotating spiral-like waves (*Fig. 18*). This model corresponds more closely to the isolated reticular nucleus in vivo, where the two-dimensional structure is preserved. It predicts that the isolated reticular nucleus may generate sustained oscillations through reversed IPSPs when sufficient neurons are interconnected to form a two-dimensional network. It is also consistent with the idea that the neurons of the thalamic reticular nucleus can initiate sequences of spindle waves in thalamocortical networks in vivo.

A role for spindle waves

The overall pattern of spindle activity alters when the cortex is present. Experimental and modelling studies have shown that corticothalamic projections cause global coherence of thalamic oscillations. The spatiotemporal properties of synchronized thalamic spindle waves became less organized when the cortex was removed (Contreras *et al.*, 1996, 1997; see Steriade, this volume). Corticothalamic–thalamocortical loops or thalamic mechanisms may also synchronize the oscillatory activity of neurons

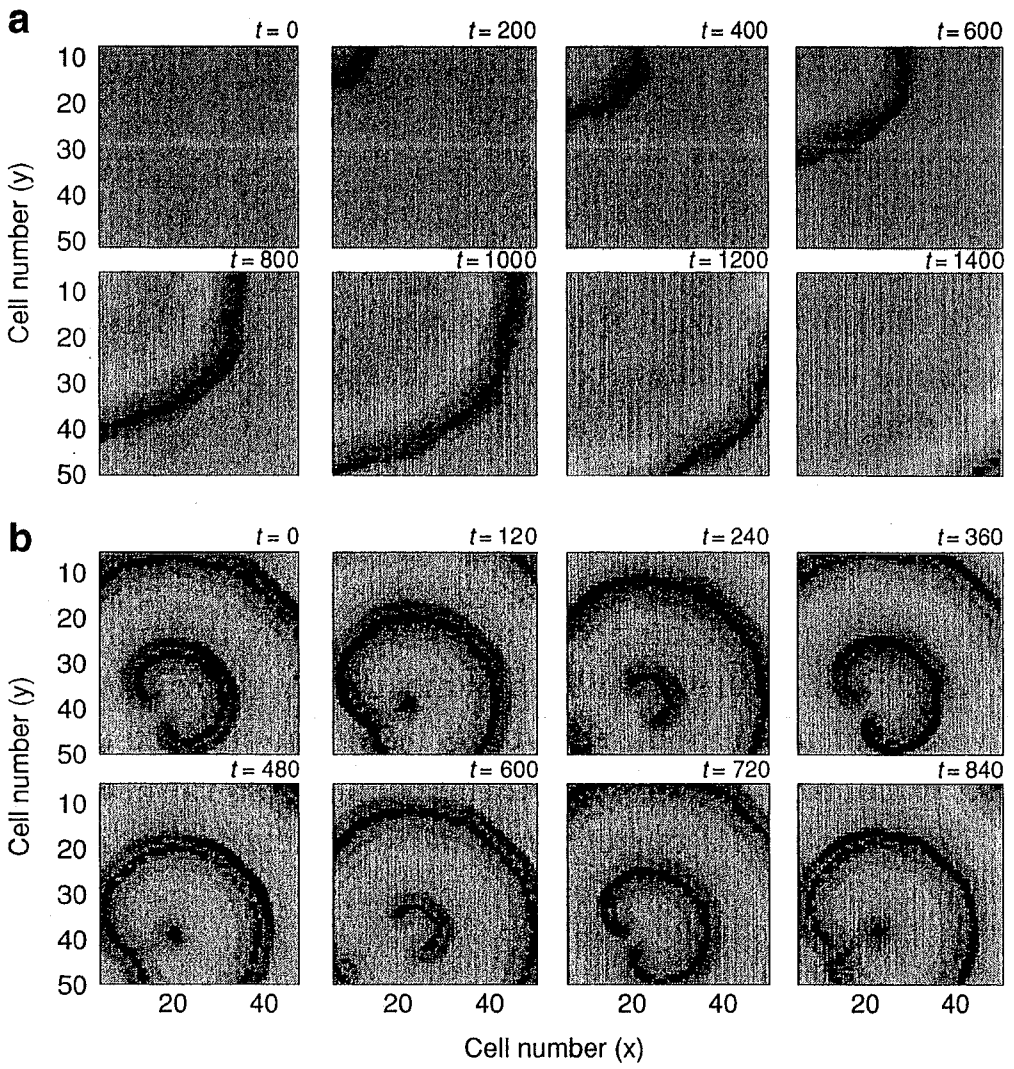

Figure 18. *Localized patterns of activity in a two-dimensional (XY) network model of 50 x 50 thalamic reticular neurons.* ***a****, the maximal conductance for the low-threshold* Ca^{2+} *current in each cell was 2.2 mS* cm^{-2}*. Initial stimulation of cell 1,1 (upper left corner) at time (t) = 0 led to a cylindrical wave travelling through the network with a constant velocity.* ***b****, increasing the maximal conductance for the low-threshold* Ca^{2+} *current to 2.45 mS* cm^{-2} *led to self-sustained activity in the form of a rotating one-arm spiral wave. Modified from Bazhenov* et al., *1999.*

in distant parts of the cortex, which were not affected by cutting horizontal intracortical connections. Thus, during non-REM sleep, the thalamus entrains the cortex with patterns of activity that are more spatially and temporally coherent than those normally present in the awake state. Synchronous spindle waves in many thalamic neurons provide a highly coherent input to the

cortical neurons, which should powerfully depolarize them. The cortex, in turn, organizes the patterns of spindle activity throughout the thalamus.

Such a powerful excitation could possibly be used to reorganize cortical networks following learning in the awake state (Wilson and McNaughton, 1994; Sejnowski, 1995). During spindle waves, Ca^{2+} currents in the dendrites brings a massive amount of Ca^{2+} into the activated thalamic and cortical neurons. The Ca^{2+} influx influences enzyme cascades and over many minutes may lead to long-term changes in the expression of genes coding for ion channels, receptors and regulatory enzymes (see Berridge, this volume). If only a small subset of cortical and thalamic neurons participate fully in generating spindle waves, the increased Ca^{2+} input would 'tag' this subset for Ca^{2+}-mediated long-term changes. The oscillatory activity during sleep could thus be a mechanism for reinforcing the connectivity of groups of cortical neurons that were active together during the preceding awake period.