A Biophysical Model of Cortical Up and Down States: Excitatory-Inhibitory Balance and H-Current

Z. Navratilova[1] and JM. Fellous[1,2,3]

[1]ARL Division of Neural Systems Memory & Aging, [2]Psychology Dept, [3]Applied Mathematics, University of Arizona, Tucson, AZ, USA

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INTRODUCTION

Background

• During slow-wave sleep (SWS), the membrane potential of neocortical neurons oscillates between two states at a frequency of ~0.5 Hz. This oscillation is highly synchronous across cortical regions, and can be seen in the local field potential .

• During the higher potential or "up" state, the neuron fires frequently. During the down state the neurons are essentially silent.

• Because of their occurrence during slow wave sleep, and their synchrony across cortical regions, up states are thought to have a role in memory consolidation.

• Up states are also observed in vitro in cortical slices, suggesting that this is a local reverberatory network phenomenon, which gets synchronized in vivo during SWS.

• A precise balance of excitation and inhibition is necessary for the generation of up states, but the data is still unclear (compare Haider et. al., 2006, Rudolph et. al., 2007 and Waters and Helmchen, 2006).

Questions

• Are up states *in vitro* really the same as up states *in vivo*? In particular, can the size of the network give an indication as to the realism of the up state?

• Are there intrinsic or network properties conducive to the start of an upstate? If so, these properties could be manipulated to study the extent to which up/down states are similar in vivo and in vitro.

Goal

• Create a simple biophysical recurrent network that generates realistic up/down states.

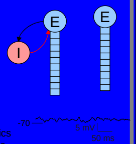
• Vary the size of the assembly in which the up-states occur. Analyze the up state characteristics

• We hypothesize that an intrinsic current such as IH, and a network property such as precisely timed inhibition can be used to modulate the probability of starting an upstate.

METHODS

• 26 'ball-and-stick' excitatory pyramidal neurons with:
  - Passive leak currents in the soma and dendrite
  - Voltage-gated Na^+, K^+ and Ca^{2+} currents in the soma
  - Ca^{2+} activated K+ channels in the soma
  - Ca^{2+} pumps and buffering in the soma

• 6 single compartment inhibitory neurons with:
  - Voltage-gated Na^+ and K^+ currents. Passive leak currents.



• Passive currents were adjusted so that input resistance is realistic, and resting membrane potential is like that of a down state *in vivo.* Sodium conductances were adjusted to give a realistic threshold for action potential generation

• An Ornstein-Uhlenbeck noise source (Destexhe et. al., 2001) in each neuron mimics inputs from neurons from outside of the network, and is optimized so that membrane potential fluctuations resemble those during a down state *in vivo*

• Probabilistic AMPA/NMDA synapses showing facilitation and depression. Deterministic perisomatic GABA synapses to create shunting inhibition.

RESULTS

2. Model Up States

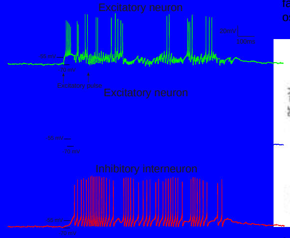
A. Optimization of the network to generate up states

• To generate an up state, a current pulse was given simultaneously to a few (~30%) excitatory neurons to mimic excitatory inputs from thalamus.

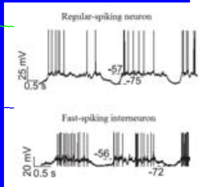
• The conductances of the synaptic inputs were adjusted to obtain up state firing rates and membrane potential fluctuations similar to those measured *in vivo*.

B. Comparison of model up states to in vivo data

Simulations



In vivo recordings of regular spiking and fast spiking neurons during the slow oscillation from Haider et. al. (2006)



C. Up state statistics

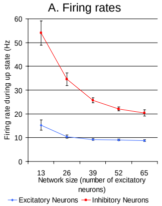
	Model	*In vivo* data
Excitatory neuron firing rates	10.4 +/-1.3 Hz	8-15 Hz
Inhibitory neuron firing rates	34.5 +/-5.3 Hz	15-30 Hz
Average Up state membrane potential	-59.7 +/-1.9 mV	-50 to -60 mV
Up state membrane potential fluctuations (standard deviation)	4.69 +/- 0.52 mV	~3 mV
Average Down state membrane potential	-68.3 +/- 0.5 mV	-65 to -75 mV
Down state membrane potential fluctuations (standard deviation)	1.03 +/- 0.20 mV	~1 mV
Duration of up state	1.168 +/- 0.470 s	0.5 – 1.5 s

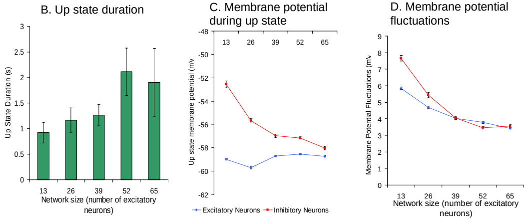
In vivo data summarized from: Sanches-Vives and McCormick, 2000; Isomura et. al., 2006; Haider et. al., 2006; Rudolph et. al., 2007; and Waters and Helmchen, 2006.

3. Model Up State Statistics and Network Size

The network size was varied while keeping the proportion of excitatory to inhibitory neurons constant, and while scaling the synaptic conductances to keep the overall levels of excitation and inhibition constant.

A. In small networks, larger EPSP size (due to larger synaptic conductances) may allow the neuron to cross threshold more often even though average input is the same.
B. Up state duration was longer for larger networks.
C. slightly higher excitatory neuron firing rates cause an increase in the number of excitatory inputs to the inhibitory neurons which gets balanced out by an increase in inhibitory inputs.
D. The size of fluctuations in excitatory neurons are mainly determined by the IPSPs.





4. Effects of H-Current on Up State Initiation

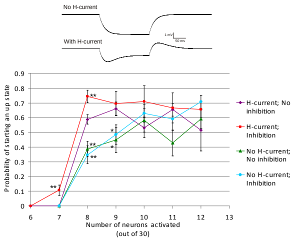
• Up states are likely to be initiated by synchronous input from the thalamus (Contreras and Steriade, 1995). The regularity of SWS oscillation may rely on currents that cause rhythmic activity or re-depolarization after the termination of an up state.

• H-currents are involved in generating rhythmic activity and are modulated by many neuromodulators and neurotransmitters (Luthi and McCormick, 1998)

• Cortistatin, a peptide expressed in the cortex and hippocampus, enhances slow wave sleep and increases the h-current (Schwietzer et. al., 2003)

•The h-current makes up-states easier to generate with simultaneous excitatory inputs.

• Because the H-current activates at hyperpolarized membrane potentials, an inhibitory pulse prior to simultaneous excitatory inputs enhances the activation of the H-current and increases the probability of generating an up state.



* p<0.05 from h-current no inhibition
** p<0.01 from h-current no inhibition

CONCLUSIONS

• A simple network with ~40 or more excitatory neurons and ~25% inhibitory neurons can generate realistic up states that terminate by themselves.

• Membrane fluctuation size, firing rates of inhibitory neurons and up state duration may be used as indicators of underlying network size.

• An H-current increases the probability of generating an up state with the same number of synchronous inputs.

• Inhibition or hyperpolarization just prior to synchronous excitatory neuron inputs makes the likelihood of up state generation even greater in the presence of the H-current.

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