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

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Abstract. During slow-wave sleep, cortical neurons oscillate between up and down states. Using a computational model of cortical neurons with realistic synaptic transmission, we determined that reverberation of activity in a small network of about 40 pyramidal cells could account for the properties of up states in vivo. We found that experimentally accessible quantities such as membrane potential fluctuations, firing rates and up state durations could be used as indicators of the size of the network undergoing the up state. We also show that the H-current, together with feed-forward inhibition can act as a gating mechanism for up state initiation.

1 Introduction

Slow wave sleep (SWS) is an active brain state in which memory consolidation and replay of neural activity patterns occur [1]. This stage of sleep is characterized by a slow (~0.5 Hz) oscillation in the cortical electroencephalogram (EEG). At the single cell level, cortical neurons switch between two states: an 'up state,' during which the membrane potential of the neurons is higher and the neurons spike frequently, and a 'down state' when the neurons are essentially silent [2, 3]. Although this oscillation can be highly synchronous between distant cortical regions (for example between the prefrontal and entorhinal cortex [4]), up states are also observed within cortical slices. *In vitro*, local glutamate application can initiate an up state in local neurons, causing a wave of up state onsets to spread across the slice [5]. In other slice preparations up states are more sporadic, but show repeating and ordered sequences of onsets [6]. Ordered up state onsets have also been observed *in vivo* [7]. Altogether, these data suggest that up states are local network phenomena that can be initiated by surrounding activity.

Up states recorded from different cortical regions do not have the same properties. For example, the firing rates of neurons may stay constant or decrease during the duration of the up state, depending on the cortical region under consideration (Andrea Hasenstaub, personal communication). Also, a precise mix of excitation and inhibition is necessary for the generation of up states, but the data on whether that mix includes more inhibition, excitation or a balanced amount is still unclear. Three groups have reported different inhibition to excitation ratios: 1:1 [8], 1:10 [9], or 2:1 [10]. The discrepancies can probably be attributed to differences in the cortical regions recorded, differences in the animal's species and differences in the induction and

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depth of sleep (anesthesia or natural sleep). Because data from different preparations are so varied, it is likely that different network properties in different cortical regions lead to different properties of up states. We hypothesize here that one of the major differences leading to differences in up states is the size of the network being recruited.

How up states are generated *in vivo* is still unknown, but it is thought that a pulse of synchronous excitation from the hippocampus [11], thalamus [12] or other cortical neurons may be key. While network activity is certainly at play, intrinsic membrane properties may synergistically contribute as well [13]. We hypothesized that the H-current may play a major role in the initiation of up states, because it is a depolarizing current that activates during rapid changes in membrane potential (such as those caused by synchronous inputs) at below-threshold potentials. It has been shown to be involved in generating some types of rhythmic activity [14]. Additionally, this current is modulated by many types of neurotransmitters, such as those activated during SWS. For example, cortistatin, a peptide expressed in the cortex and hippocampus, increases the H-current and enhances slow wave sleep [15]. Also, dopamine enhances the amplitude and shifts the activation curve of this current [16]. Thus, we hypothesized that the H-current will enhance the likelihood of up state initiation.

2 Methods

We used the simulator NEURON to create a network model of biophysical neurons. Two types of neurons were simulated: excitatory, pyramidal-like neurons, and inhibitory GABAergic neurons. The excitatory neurons had a single somatic compartment, and a dendrite comprised of ten compartments. Passive leak currents adjusted to give an input resistance of 90 MΩ, were inserted in all compartments. Voltage-gated sodium and potassium currents were added to the soma [17] and adjusted to give an action potential generation threshold of -53mV. To control the bursting properties of pyramidal neurons, a calcium-activated potassium channel [18] and a calcium channel, pump and buffering [19] were added to the somatic compartment. In some simulations (see results, Fig. 3), an H-current was added to all compartments, comparable with experimental data [20]. Inhibitory neurons consisted of a single somatic compartment, and included voltage-gated sodium and potassium currents and passive leak currents adjusted to give an input resistance of 150 MΩ.

An Ornstein-Uhlenbeck background synaptic noise source [21] was added to the soma of each neuron to mimic the inputs from neurons outside of the simulated network, and was adjusted so that membrane potential fluctuations resembled those during a down state *in vivo*. Pyramidal neurons were connected to each other with AMPA/NMDA synapses showing facilitation and depression. These synapses were positioned onto a random dendritic compartment. There were approximately four times fewer inhibitory neurons than pyramidal neurons. Each inhibitory neuron received inputs from all the pyramidal neurons and output onto the somatic compartment of each pyramidal neuron to create shunting of the currents from the dendrite. These GABAergic synapses were deterministic [22]. Interneurons were not interconnected.

3 Results

A network of 26 pyramidal neurons and 6 inhibitory neurons was created as specified above. To generate an up state, a short (150ms) current pulse was given simultaneously to a few (~30%) model pyramidal neurons to mimic excitatory inputs from the thalamus, another cortical region, or the hippocampus. The conductances of the synaptic inputs were adjusted to obtain up state firing rates and pyramidal neuron membrane potential (V_m) averages and fluctuations (standard deviation) similar to those measured *in vivo* (Fig. 1 and Table 1). The V_m fluctuations were the only statistic that did not fit to measured data levels if this network were to generate up states, and so conductances were adjusted to make it as low as possible. The resulting up states terminated spontaneously after 500-2000 ms. Firing rates towards the end of the up state were constant until there was an abrupt end, indicating that activity did not just peter out.

Table 1. Comparison of up state statistics in model with *in vivo* data [4], [7], [8], [9], [10]

	26 excitatory neuron 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	4.69 +/- 0.52 mV	2-3 mV
Average down state membrane potential	-68.3 +/- 0.5 mV	-65 to -75 mV
Down state membrane potential fluctuations	1.03 +/- 0.20 mV	0.6-2 mV
Duration of up state	1.168 +/- 0.470 s	0.4 – 1.6 s

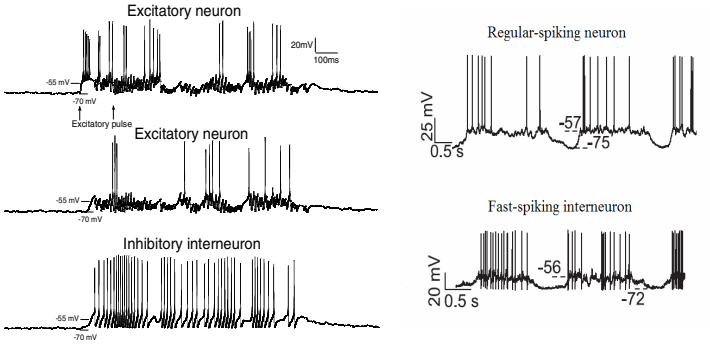

Fig. 1. Membrane potentials of three neurons (two pyramidal and one inhibitory) during an example up state generated by the model (*right*) compared to in vivo recordings of regular spiking and fast spiking neurons during the slow oscillation [8] (*left*)

To investigate how network size affected up state statistics, it was varied while keeping the proportion of excitatory and inhibitory neurons constant. Synaptic conductances were scaled proportionately to keep the overall synaptic inputs to each neuron approximately constant. This kept the average V_m of pyramidal neurons during up states constant (Fig. 2A), but changed the V_m fluctuations (Fig. 2B), which

were mainly determined by the conductances of single synaptic events. The V_m fluctuations reached the measured *in vivo* level at a network size of 39 excitatory neurons, and appeared to asymptote within the *in vivo* measured range. The firing rates of both excitatory and inhibitory neurons during up states were larger in small networks (Fig. 2C). This may be due to the larger size of each individual synaptic conductance, which may allow the neuron to cross threshold more often even though the average input is approximately the same. The average V_m of inhibitory neurons, unlike that of pyramidal neurons, increased as network size decreased (Fig. 2A). This increase may be due to the slightly higher pyramidal neuron firing rates in the smaller networks, which cause a non-balanced increase in the number of excitatory inputs to the inhibitory neurons. Another statistic that changed with network size was up state duration, which increased for larger networks (Fig. 2D). These results show that a relatively small number of cells (39 pyramidal neurons, and 9 interneurons) can be recruited to generate and sustain up states comparable to those observed *in vivo*. Smaller networks required larger individual synaptic events than those observed *in vivo* to generate an up state.

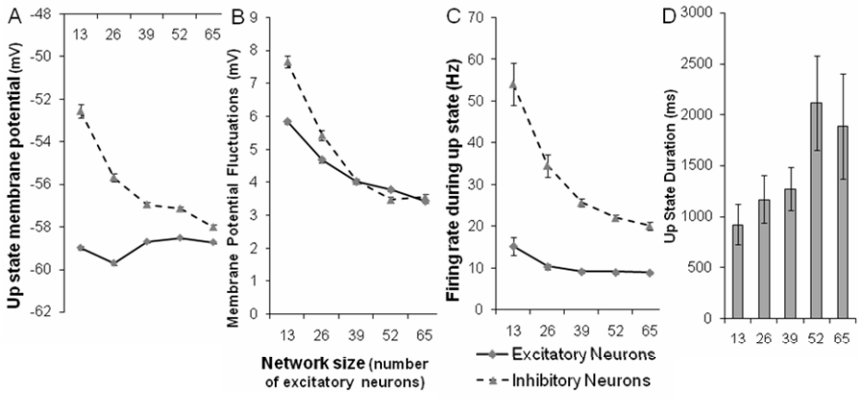

Fig. 2. The effects of changing network size on up state membrane potential (*A*), fluctuations (*B*), and firing rates (*C*) of both types of neurons in the network, and duration of the up state (*D*). *X-axis* is the number of pyramidal (excitatory) neurons in the network.

To test our hypothesis that intrinsic currents such as the H-current could contribute to the initiation of up states, we added this current to the pyramidal neurons in a 30-pyramidal neuron network. The H-current made up states more likely to be initiated by simultaneous excitatory inputs (Fig. 3, solid line compared to dotted line). Because the H-current activates at hyperpolarized membrane potentials, we reasoned that an inhibitory volley prior to excitatory inputs could further facilitate the elicitation of the up state. Such inhibition prior to excitation indeed enhanced the activation of the H-current and increased the probability of generating an up state (Fig. 3, dashed line). These differences in up state initiation were even bigger in a smaller network, where fewer simultaneously active neurons were needed to activate an up state (data not shown). The H-current did not have an effect on other properties of up states, such as their firing rates or duration.

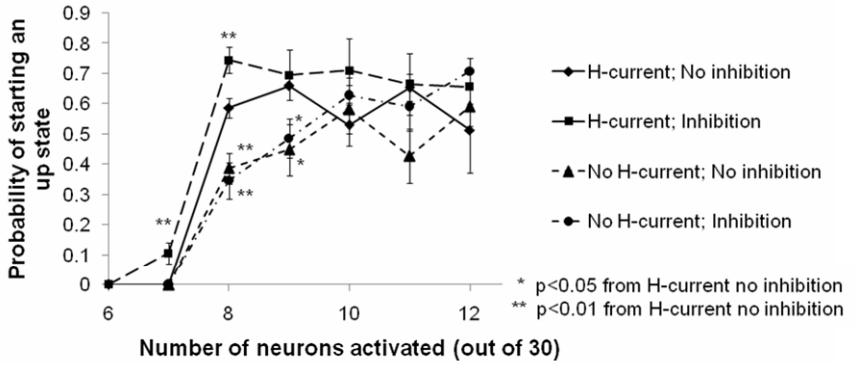

Fig. 3. The effects of the H-current in pyramidal neurons (*solid and dashed lines*), and an inhibitory volley prior to excitatory input (*dashed and dash-dotted lines*) on the probability of up state initiation. *Dotted line* is the control network, with no H-current or inhibitory volley.

4 Conclusions

Our model indicates that up states can be generated in a small network (as little as 40 neurons, if the network is fully connected) by the brief activation of a subset of those neurons. Activity reverberates in the network and spontaneously and abruptly shuts off, in the time scale seen *in vivo*. Also as seen *in vivo*, particular ratios of excitatory and inhibitory conductances were conducive to initiating up states.

In our model V_m fluctuation amplitudes, firing rates during the up state and up state duration all varied monotonically with network size. These experimentally measurable quantities can therefore be used as indicators of the size of the network (assuming full connectivity) that is responsible for an up state in preparation in which network size is not directly experimentally accessible. Thus, models such as this one can in principle be used to distinguish between different types of up states in different preparations and help determine the differences in their underlying mechanisms.

We further showed that adding an H-current increased the probability of generating an up state with the same number of synchronous inputs. Thus, the H-current may be one of the factors that enhance the initiation of up states. Feed-forward inhibition or hyperpolarization just prior to synchronous excitatory inputs made the likelihood of up state generation even greater in the presence of the H-current. This result suggests that feed-forward inhibition just prior to synchronous excitatory inputs could increase the likelihood of up state generation, and act as a gating mechanism. The neuromodulation of the H-current during SWS may be one of the factors that allows and/or enhances the initiation and gating of up states.

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