# The Role of Mitral Cells in State Dependent Olfactory Responses

*Trygve Bakken & Gunnar Poplawski*

*BGGN 260 Neurodynamics*
*Winter 2008*

## Abstract

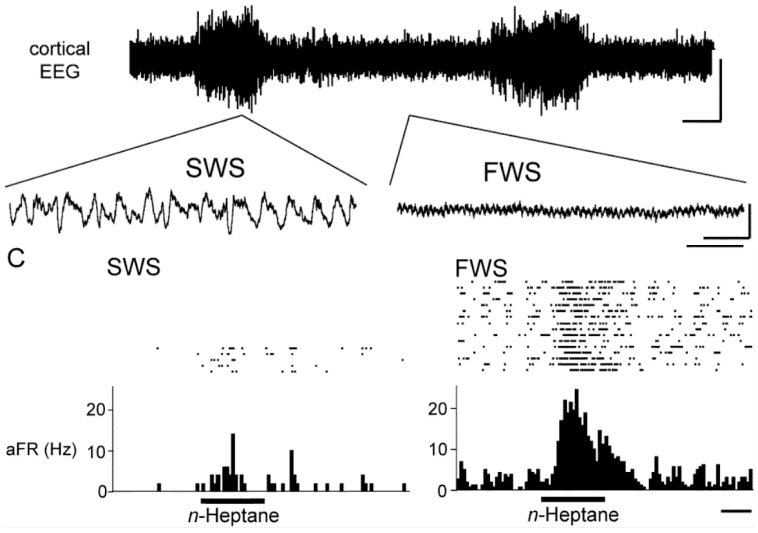
Many behavioral studies have shown a reduced responsiveness to a variety of sensory stimuli in sleep versus awake states. In this study, we are concerned with how the brain changes its response to odor stimuli as a function of the sleep state of the organism. During slow wave sleep state (SWS), studies have shown reduced synaptic transmission of sensory signals through thalamocortical neurons. However, olfactory information uniquely does not relay through the thalamus, and so must be gated elsewhere. Murakami et al showed sleep state dependence of some mitral cells in the olfactory bulb of anesthetized rats. We attempted to reproduce this behavior *in silico* with a morphologically and electrophysiologically realistic four compartment model of a mitral cell. Mitral cell response to an odorant depended on the phase, magnitude and decay rate of both glomerular stimulation and dendrodendritic inhibition. This model also exhibited fast and slow wave states that altered the phase shift of subthreshold oscillations in response to an odor stimulus. These effects do not provide a convincing mechanism for gating olfactory responses at the level of an individual mitral cell, but they may contribute to network interactions between many mitral and granule cells in the olfactory bulb that collectively exhibit this gating behavior.

## Introduction

Many behavioral studies have shown a reduced responsiveness to a variety of sensory stimuli in sleep versus awake states. For example, Carskadon et al demonstrated that human subjects had a significantly reduced response to two odorants (peppermint and pyridine) in state 4 versus state 1 sleep (Carskadon and Herz 2004). Presumably conscious awareness of odors requires information to be transmitted from peripheral sensory structures to the cortex. How does the brain change its response to odor stimuli as a function of the sleep state of the organism?

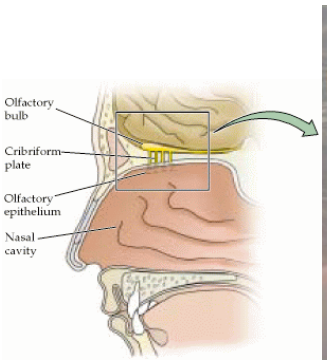
In order to answer this question we first need a more precise definition of brain state during sleep. Dynamic cortical networks show a transition between different oscillatory firing states. These neural oscillations are a key feature of cortical networks and can be broadly classified as slow run or fast run. Many cortical structures show transitions between these oscillatory states. For example, during an epileptic seizure the brain transitions between slow bursting and fast tonic firing states. There are also state transitions between different sleep states, such as slow wave sleep and rapid eye movement or wakening. Electroencephalography (EEG) reveals the distinct electrical signature of synchronized neural activity during different sleep states.

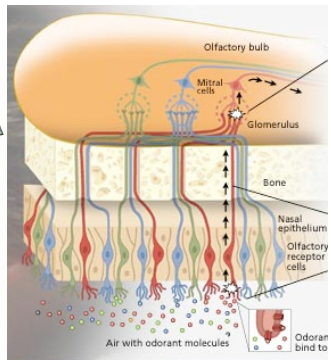
Using EEG to monitor the brain state of anesthetized rats, Murakami et al could investigate the neural mechanisms that lead to the state dependent gating of the olfactory system. (Murakami, Kashiwadani et al. 2005) They were interested in this question because the olfactory circuitry uniquely bypasses the thalamus, which acts as a relay for most sensory systems to the neo-cortex. During slow wave sleep state (SWS), studies have shown reduced synaptic transmission of sensory signals through thalamocortical neurons. Therefore, the gating must occur at a different location in the olfactory tract. They measured the response of rat olfactory cortex neurons to an odorant stimulation during slow and fast wave states. They found a significantly reduced cortical response during SWS in all but three neurons. They also saw a reduced response in 25% of mitral cells recorded in the olfactory bulb, but they concluded that this gating was not necessary for the reduced cortical response.

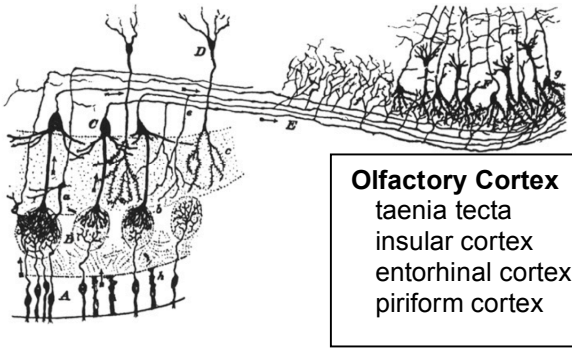



(Murakami, Kashiwadani et al. 2005)

In order to understand this result, it is helpful to have an overview of the olfactory system to put these mitral cells in the context of their local circuitry:



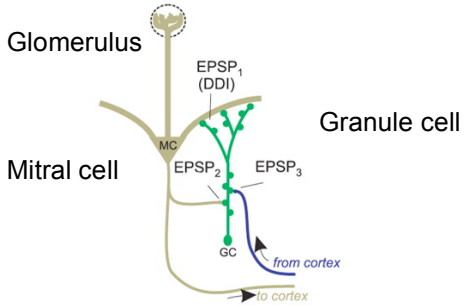



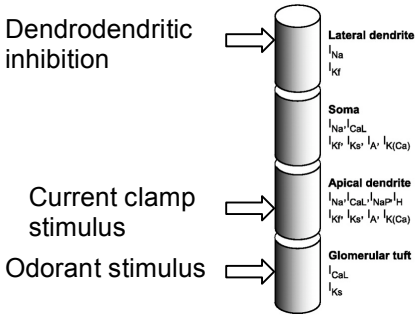
**Olfactory Cortex**
taenia tecta
insular cortex
entorhinal cortex
piriform cortex

Odorants enter the nasal cavity upon inhalation and bind olfactory receptors in sensory neurons sitting in olfactory epithelium. All neurons that express the same receptor type project through the cribiform plate of the skull into a single glomerulus where they synapse on mitral and periglomerular cells. (Fabio Marques Simoes de and Gabriela 2007) Here the odor response is tuned by, for example, regulating mitral cell spike initiation. (Aungst, Heyward et al. 2003) In the next layer of the glomerulus, mitral and granule cells interact bidirectionally via dendrodendritic synapses. This circuit has been implicated in the control of mitral cell spike synchronization, network local field potential oscillations and the dynamics of olfactory bulb responses to odorants. (David, Linster et al. 2007)

We attempted to replicate Murakami's *in vivo* findings in a computational model of a mitral cell. Then, we hoped to leverage the flexibility of an *in silico* model to try to understand the properties of a mitral cell and its inputs that lead to the state dependent gating of its response to a stimulus.




(Balu, Pressler et al. 2007)




(Rubin and Cleland 2006)

Olfactory cortex sends projections to granule cells in the olfactory bulb which then inhibit mitral cells at dendrodendritic synapses. This connection may provide mitral cells with information about the state of other cortical regions, for example a global slow or fast wave state seen in different sleep stages. Therefore, we tested the effect of granule cell inhibition of the mitral cell lateral dendrite as a model for cortical feedback.

In our experiment, we used Rubin and Cleland's mitral cell model that they based on the morphologically and electrophysiologically precise 286 compartment model of Bhalla and Bower (1993). It incorporates 18 ion channels distributed across four compartments, and the parameters were adjusted to match known mitral cell behavior through 2005.

## Results

To simulate the slow wave state (SWS) and the fast wave state (FWS) found in cortical neurons in the mitral cell model we had to alter the membrane resting potential. This was achieved by injecting different currents into the apical dendrite via the simulation of a current clamp. The mitral cell model shows an intrinsic subthreshold oscillation of the membrane voltage. A stronger injected current leads to an increase in membrane voltage and displays a higher frequency for the subthreshold oscillations. Unfortunately the mitral model failed to be tuned after in vivo data from neurons of the olfactory cortex, so we defined the SWS with subthreshold oscillations at 20 Hz and the FWS with subthreshold oscillations at 30 Hz (cortical neurons in vivo: 1 Hz and 4 Hz respectively) (Rubin and Cleland 2006). Figure 1 shows the membrane voltage time course of the SWS and FWS of the mitral cell model.

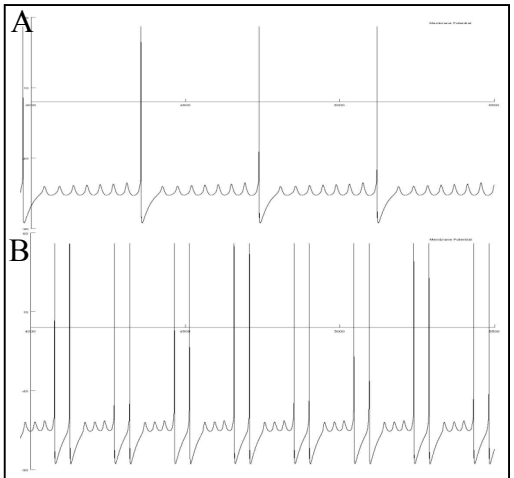



**Fig.1:** membrane voltage time course of subthreshold oscillations achieved by injecting different currents that raise the membrane voltage to **A** – 64mV in the SWS (20Hz) and **B** -62mV in the FWS (30Hz)

To simulate an odor stimulus, we constructed an excitatory synapse on the glomerular tuft. To simulate a realistic odor stimulus we applied a 0.01μS, 0mV excitatory current with a 50ms decay. Excitation of the glomerular tuft by the odor stimulus in the FWS showed different responses than in the SWS. As shown in Figure 2, the stimulus during FWS causes a response of two spikes after the synaptic excitation followed by recovery of the normal subthreshold oscillations. During the SWS in contrast, we observed a spike inactivation after a singe spike response to the excitatory stimulus.

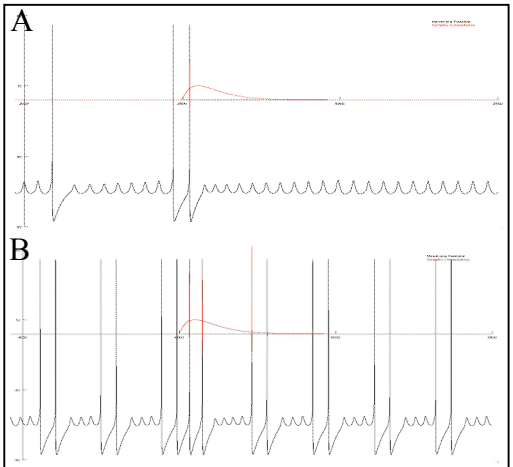



**Fig.2:** membrane voltage time course before and after excitatory synaptic odorant stimulus (red: synaptic conductance) to the glumarular tuft during **A** SWS and **B** FWS.

This spike inactivation might be a consequence of an intrinsic signal damping property of the mitral cell, thereby silencing signal transduction to the olfactory cortex during SWS.

To further characterize the mitral cell response to the odor stimulus in the FWS, we investigated the phase dependency of the stimulus by varying the onset time of the excitatory synaptic input into the glomerular tuft. Figure 3 shows that a late onset leads to an increased response of the mitral cell to the odor stimulus. In this case we observe four instead of three spikes as seen in the early onset. This behavior can be explained by the spiking initiated by the subthreshold oscillations of the mitral cell in FWS. If the odorant stimulus occurs between these spikes, the excitatory effect is not as prominent as when the stimulus occurs during a subthreshold oscillatory spiking phase.

This observed behavior gives hints to the importance of timing of these events. Mitral cells have also been described to have a very important role in synchronizing the synaptic input from many different olfactory epithelial neurons (David, Linster et al. 2007).

To investigate the possibility of a feed back or feed forward mechanism from the olfactory cortex to the mitral cell, which regulates the signal transductions properties of the mitral cell to the olfactory cortex during SWS and FWS, we simulated an inhibitory synapse on the lateral dendrite of the mitral cell during odor stimulus. This inhibitory synapse in our model is simply defined by its parameters. In an vivo situation, or in an computational model of higher order, a granule cell would receive an excitatory or inhibitory input from the olfactory cortex and activate an inhibitory synapse on the lateral dendrite of the mitral cell. We investigated the inhibition in both the FWS (Figure 4) and the SWS (Figure 5).

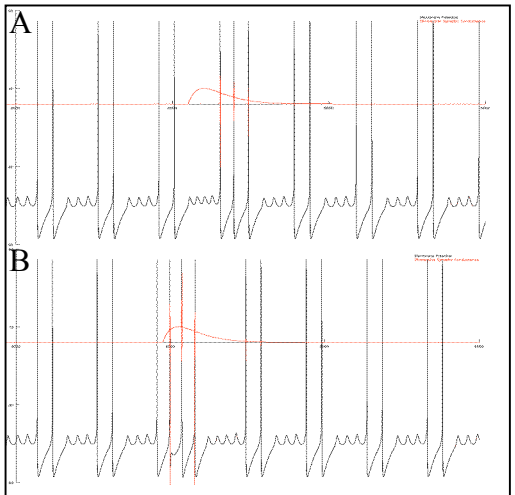



**Fig.3:** Membrane voltage time course before and after excitatory synaptic odorant stimulus (red: synaptic conductance) to the glumarular tuft with **A** an early onset (between subthreshhold oscillatory spikes) and **B** a late onset (during subthreshhold oscillatory spikes) in FWS.

In figure 4 we investigated the influence of synapse number/strength on the transmitted stimulus. We could observe that the odorant stimulus is very robust in terms of spike number to the inhibition strength. If we increase the inhibitory synapse strength from 0.05uS to 1uS, all we observe is a phase shift of the spikes caused by the odor stimulus. This simulation shows again, that the mitral cell function in signal transduction to the cortex is more of a phase synchronizing nature than a on/off switching one.

A different influence of the inhibitory synapse can be observed during SWS. In Figure 5 we applied the inhibitory synapse before (Figure 5 B), after (Figure 5 C) and synchronal with the odor stimulus. In all cases the inhibitory stimulus causes a rescue of the subthreshold oscillatory pattern, which was diminished during odor stimulation (see Figure 2A. This rescue of oscillatory behavior of the mitral cell might be a hint of a regulatory system from the olfactory cortex.

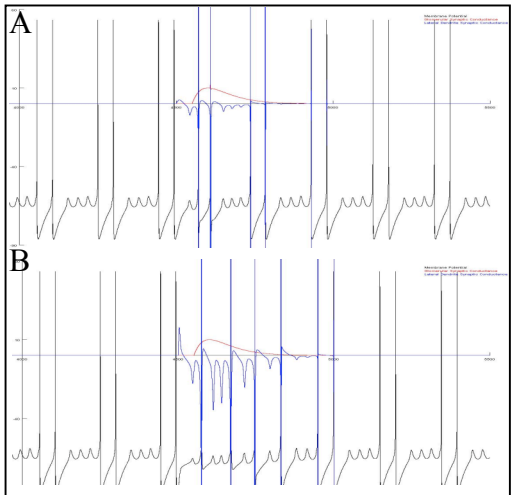



**Fig.4:** Membrane voltage time course before and after excitatory synaptic odorant stimulus (red: synaptic conductance) to the glumarular tuft and inhibitory synaptic stimulus to the lateral dendrites with **A** a few synapses (gMax = 0.05uS) and **B** many synapses (gMax = 1 uS) during FWS.

During FWS the activation of the inhibitory synapse leads to shifting of the odor stimulus provoked response, while during SWS the silenced odor stimulus response is reactivated by the inhibitory input. Giving the olfactory cortex neurons the possibility to trigger the throughput of olfactory responses during SWS, or rather (which has to be investigated in the future) during the switch between SWS and FWS.

Finally, we quantified the phase dependence of the mitral cell membrane voltage response to an inhibitory input in the presence and absence of an odor stimulus. Latency is the

time between onsets of inhibition and an action potential, while shift is the time between onsets of the action potential with and without inhibition. Subthreshold oscillation maxima are at 0 and 2π and minimum at π. Inhibition has a maximal effect when it occurs on the decreasing slope of the oscillations, and this effect is exaggerated when an excitatory input is present (as seen by the peaks of the dashed lines below). This makes sense because the inhibition helps hyperpolarize the cell more and thereby reduces the probability of spiking.

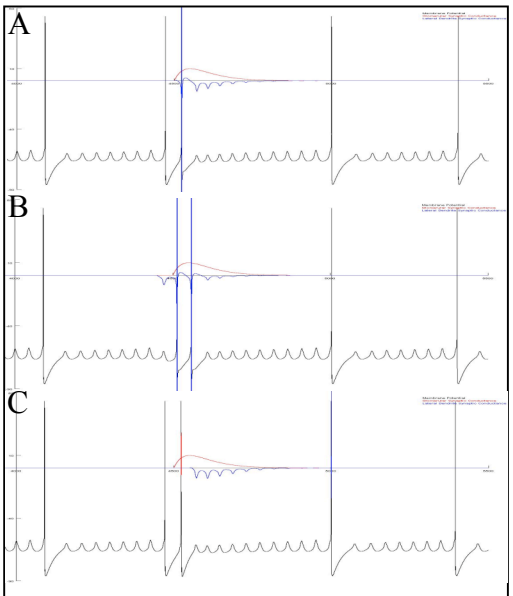



**Fig.5:** Membrane voltage time course before and after excitatory synaptic odorant stimulus (red: synaptic conductance) to the glumarular tuft and inhibitory synaptic stimulus to the lateral dendrites with **A** simultaneous excitatory and inhibitory stimulation, **B** Inhibitory input prior to odorant stimulation and **C** Inhibitory feedback after odorant stimulation

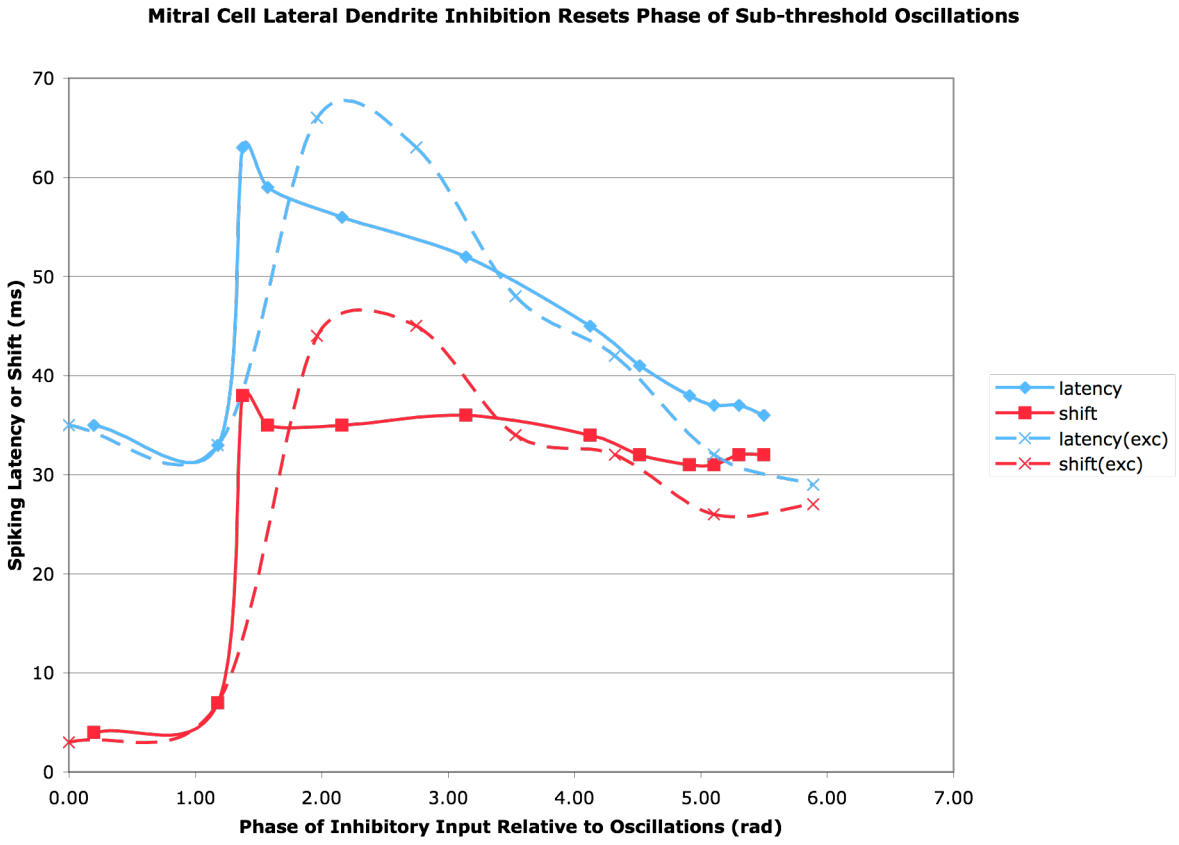



**Fig. 6:** Phase dependence of mitral cell membrane voltage response to an inhibitory input with and without an odor stimulus. Latency is the time between onsets of inhibition and an action potential. Shift is the time between onsets of the action potential with and without inhibition. Subthreshold oscillation maxima are at 0 and 2π and minimum at π.

## Discussion and Future Work

This mitral cell model exhibits fast and slow wave states that alter odor stimulus response. Mitral cell response to an odorant depends on the phase of both stimulation and dendrodendritic inhibition. We found a specific case where the mitral cell is suppressing the odor stimulus input by intrinsic properties. This suppression can be reversed by several inhibitory feedbacks of the olfactory cortex. The magnitude and decay rate of inhibition also change the mitral cell response. These effects do not provide a convincing mechanism for gating olfactory responses at the level of an individual mitral cell, but they may contribute to network interactions between many mitral and granule cells in the olfactory bulb that collectively exhibit this gating behavior.

While this model has over 50 free parameters it would be interesting to track down which were contributing to these effects. For example, it is thought that the ATP potassium channel prevents the mitral cell from spiking too frequently in order to protect it from excitotoxicity resulting from damaged olfactory sensory neurons dumping glutamate onto glomerular synapses. It would also be interesting to model trains of odor stimuli and inhibitory inputs and to calculate the magnitude and reliability of mitral cell responses in SWS versus FWS.

## References


Aungst, J. L., P. M. Heyward, et al. (2003). "Centre-surround inhibition among olfactory bulb glomeruli." Nature **426**(6967): 623-9.

Balu, R., R. T. Pressler, et al. (2007). "Multiple modes of synaptic excitation of olfactory bulb granule cells." J Neurosci **27**(21): 5621-32.

Carskadon, M. A. and R. S. Herz (2004). "Minimal olfactory perception during sleep: why odor alarms will not work for humans." Sleep **27**(3): 402-5.

David, F., C. Linster, et al. (2007). "Lateral dendritic shunt inhibition can regularize mitral cell spike patterning." J Comput Neurosci.

Fabio Marques Simoes de, S. and A. Gabriela (2007). "Biophysics of olfaction." Reports on Progress in Physics(3): 451.

Murakami, M., H. Kashiwadani, et al. (2005). "State-Dependent Sensory Gating in Olfactory Cortex." Neuron **46**(2): 285-296.

Rubin, D. B. and T. A. Cleland (2006). "Dynamical mechanisms of odor processing in olfactory bulb mitral cells." J Neurophysiol **96**(2): 555-68.