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STABLE FREQUENCY RESPONSE TO VARYING STIMULUS INTENSITY IN A MODEL OF THE RAT OLFACTORY BULB

Thomas Voegtlin(1), Corinne Amat (2), Virginie Briffaud (2), Nathalie Buonviso (2), Emmanuelle Courtiol (2), Nicolas Fourcaud-Trocmé (2).

(1) Equipe Cortex, INRIA Lorraine; Vandoeuvre-les-Nancy, France
(2) Equipe Neurosciences et Systèmes sensoriels, CNRS UMR 5020, Lyon, France

ABSTRACT
In the rat olfactory bulb (OB), fast oscillations of the local field potential (LFP) are observed during the respiratory cycle. Gamma-range oscillations (60Hz) occurat the end of inspiration, followed by beta-range oscillations (15-20Hz) during exhalation. These oscillations are highly stereotyped, and their frequencies are stable under various conditions. Here we investigate the effect of stimulus intensity on activity in the OB. Using a double canulation protocol, we show that, although the frequency of the LFP oscillation does depend on the respiratory cycle, it is relatively independent from the intensity of odorant stimulation. In contrast, we found that the individual firing rate of mitral OB cells changes greatly with the intensity of the stimulation. Using a computer model of the OB, where fast oscillations are generated by the interplay between excitatory mitral/tufted cells, and inhibitory granule cells, we found that the difference between individual and population responses can be explained by the role of sub-threshold oscillations in the MCs. Sub-threshold oscillations of the MCs stabilize the frequency of the population oscillation, and allow their firing rate to vary without affecting the population frequency.

KEYWORDS
Olfaction, oscillations, spiking neurons.

1. Introduction

The rat olfactory bulb (OB) is a rich and complex sensory processing system that shows stimulus-induced properties such as neural synchronization and oscillations of the Local Field Potential (LFP). These properties are observed in other sensory systems, and they are believed to be important for neural information processing.

Recent experiments revealed the existence of two oscillation regimes in the OB of anaesthetized rats during odorant stimulation [1]. During inhalation, the LFP shows power in the gamma-frequency range and poor activity in the beta-frequenciy range, while exhalation yields strong activity in the beta-frequency range, and much less activity in the gamma range.

Oscillations in the OB are believed to originate from the interplay between excitatory and inhibitory neurons. Excitatory neurons are the mitral and tufted cells (MCs), and inhibitory neurons are the granule cells (GCs). Sensory inputs from olfactory receptor neurons (ORN) are conveyed to the MCs via glomeruli. MCs excite GCs through dendro-dendritic synapses, which in turn inhibit the MCs. This local loop is believed to induce the gamma oscillation [2]. In addition, another loop passes through the olfactory cortex (OC). MCs project axons to the OC, and pyramidal cells of the OC in turn excite GC somata. Cortical feedback is likely to play a role in the generation of beta rhythms. Beta oscillations can be observed only if the OB-OC connection is intact [3,4].

The mechanism that controls the frequency of the LFP oscillation is not understood yet. One difference between beta and gamma epochs is the amount of excitation received by the ORNs; ORNs are more excited during inspiration than during exhalation. Can the different amount of excitation be responsible for the change of oscillation frequency during respiration ?

In order to test this hypothesis, we recorded mitral cells activities and LFP in anaesthetized animals, while varying stimulation intensity. We found that LFP frequency does not depend on stimulus intensity, for both beta and gamma episodes; in contrast, we found that the activity of individual cells greatly changes with the intensity of the stimulus; the number of spikes per second increases with the intensity of stimulation.

We reproduced these experimental results in a computer model of the OB, where individual mitral cells do not fire on each cycle of the oscillation; in this model the firing rate is decorrelated from the frequency of the population oscillation.

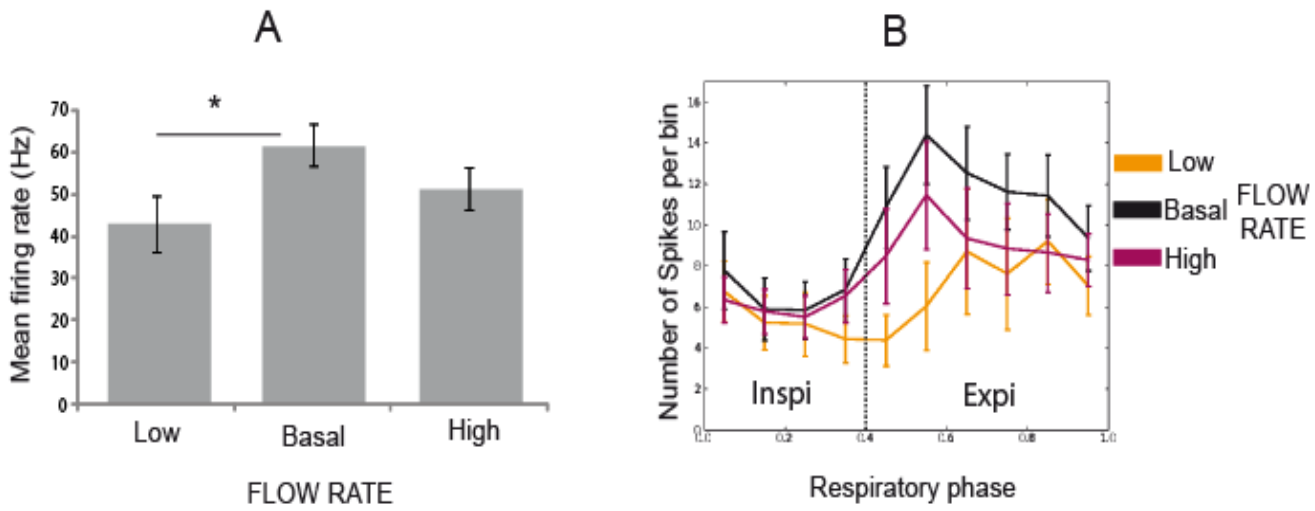

Figure 1 : A) Mean firing frequencies of mitral cells under three flow rate conditions. B) Mean instantaneous frequencies of mitral cells as a function of the respiratory cycle. n=36

2. Experimental results

In order to mimic variations in sensory input to the OB, we used a double canulation protocol, which allows us to uncouple odorant stimulation from the animal's breathing. Thus, we were able to deliver odorant stimulation in 3 different flow rate conditions: low (200ml/min), basal (500ml/min) and high (800ml/min) resulting in a low, medium and high intensity in sensory input respectively.

We observed that the number of gamma oscillatory bursts significantly increased when the flow rate was increased (low vs basal, $p < 0.01$; basal vs high, $p < 0.001$, Wilcoxon test), while the number of beta oscillatory bursts significantly decreased (low vs basal, $p < 0.001$; basal vs high, $p < 0.001$, Wilcoxon test). However, the intrinsic characteristics of oscillations, such as duration, amplitude and frequency, were not modified, except for the duration and amplitude of gamma episodes, which were significantly decreased when flow rate was decreased. Data are presented in Table 1.

Thus, the intrinsic characteristics of LFP oscillations are very stable : In particular, gamma and beta frequencies do not change with sensory input intensity.

In contrast, such stability was not observed in mitral cell individual activities. Indeed, we observed that a low flow rate induced a significantly lower percentage of responsive mitral cells (low: 66.7% vs. basal: 88.9 %; Chi^2 test, $p < 0.05$). No significant difference was observed between basal and high flow rate conditions (basal: 88.9% vs high 91.7%, $p > 0.05$).

When comparing the mean instantaneous firing frequency under the three flow rate conditions (Fig. 1A), we observed that while it reached 61.58 and 51.26 Hz under the basal and high flow rate conditions respectively, it was significantly decreased under the low flow rate condition (42.89 Hz). Fig. 1B shows the mean instantaneous frequency of mitral cells as a function of the respiratory cycle under each flow rate condition. A significant difference of distribution between low and basal conditions was observed.

		Beta	**Gamma**
Characteristics	**Flow rate**	Average *(±SEM)*	Average *(±SEM)*
Duration (s)	Low	0.242 *(±0.016)*	0.101 *(±0.008)*
	Basal	0.209 *(±0.014)*	0.135 *(±0.011)*
	High	0.215 *(±0.163)*	0.132 *(±0.011)*
Amplitude (Arbitrary unit)	Low	9.137 *(±0.804)*	9.544 *(±0.677)*
	Basal	9.446 *(±0.846)*	12.479 *(±1.802)*
	High	8.548 *(±1.113)*	9.871 *(±1.134)*
Frequency (Hz)	Low	15.900 *(±0.462)*	52.821 *(±1.035)*
	Basal	16.949 *(±0.576)*	53.749 *(±1.273)*
	High	14.912 *(±0.560)*	54.656 *(±1.108)*

Table 1: Means (± SEM) of LFP intrinsic characteristics. Duration (second), amplitude (arbitrary units) and frequency (hertz) are presented for beta and gamma oscillations and for the three flow rate conditions. Data from low and high flow rate conditions were compared to data from the basal flow rate condition (n = 23 trials). Statistical test: Wilcoxon, *p < 0.05.

3. Computer simulations

The fact that individual firing rate of the MCs are independent from the intensity of odorant stimulation suggests that the frequency of the population oscillation does not depend on the firing rate of individual cells., but on intrinsic characteristics of the mitral-granule cells network.

In order to investigate this hypothesis, we designed a computer model of the OB inspired from [5]. In this model, the frequency of the population oscillation can be much higher than individual firing rates; a given neuron does not fire on each cycle of the oscillation.

3.1 Modeling mitral cells

The membrane potential of a typical mitral cell is shown in Figure 2. The cell emits bursts of action potentials, followed by periods where the membrane potential oscillates below the firing threshold of the cell.

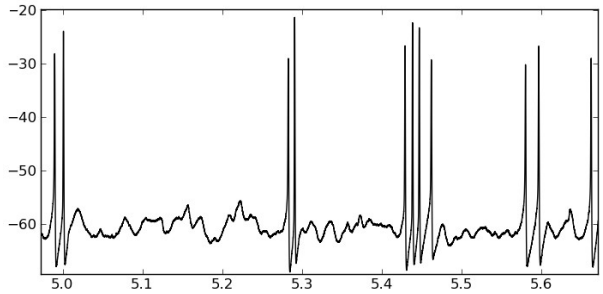

Figure 2 : Raw intracellular recording of a typical mitral cell (time in sec).

In order to model this type of neuron, we used a conductance model following Hodgkin-Huxley kinetics. The mitral cell had two sodium currents (Na, Nap) and three potassium currents (KF, KS, KA). Parameters were adapted from [6] and [7].

The membrane potential of a model mitral cell receiving a noisy input current is shown in Figure 3.

The cell emits bursts of spikes in response to a noisy input current. Between bursts, a subthreshold oscillation of the membrane potential is visible. This subthreshold oscillation is caused by the interaction between persistent Na and KS currents; it is qualitatively similar to the recording of Figure 2.

When increasing the intensity of the stimulation, we observe that the bursts last longer, and that they have more spikes. However, this does not change much the inter-spike interval inside a burst, which is approximately equal to the period of the subthreshold oscillation.

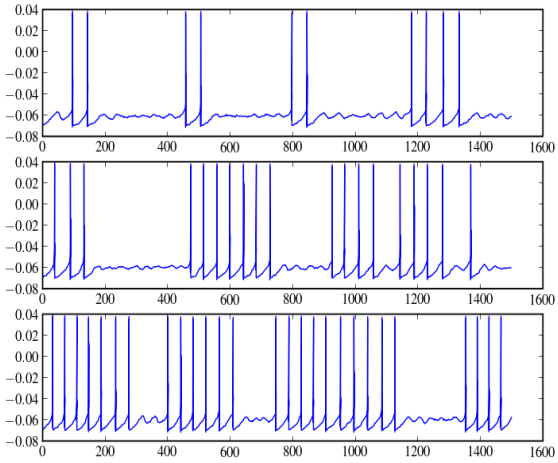

Figure 3 : Mitral cell response to a noisy input current of varying intensity. Top : I = 0.004 A/m2. Middle : I = 0.006 A/m2. Bottom : I = 0.008 A/m2.

3.2 Modeling the OB network : graded inhibition between granule and mitral cells.

Following [5], granule cells were modeled using a two compartment model : Granule cells had a dendritic compartment and a somatic compartment. Both compartments were modeled as leaky and passive; they did not have active ion channels.

Dendro-dendritic inhibition from granule to mitral cells was modeled using graded synapses, as in [5]. In this model, the probability of release of neurotransmitters by the synapse is a sigmoidal function of the presynaptic potential. In order to ensure that the membrane potential oscillates around the activation potential of the graded synapse, the leak potential of the granule cell was set slightly lower than the activation potential of the synapse.

We simulated a network of 100 mitral cells connected to one granule cell. Figure 4 shows the result of a network simulation. We observe that the network generates fast oscillations. The top row shows the membrane potential of one mitral cell (left), and the activity of all mitral cells (right). The bottom row shows the membrane potential of the granule cell (right) and the voltage-dependent probability for synaptic channels to be open in the graded synapse (left).

The first trace shows that a typical mitral cell does not fire on every cycle of the oscillation. However, the frequency of the population oscillation matches the subthreshold oscillation of the cell. This suggests that although the oscillation is a population effect, its frequency is controlled by the instrinsic frequency of subthreshold oscillations in the mitral cells.

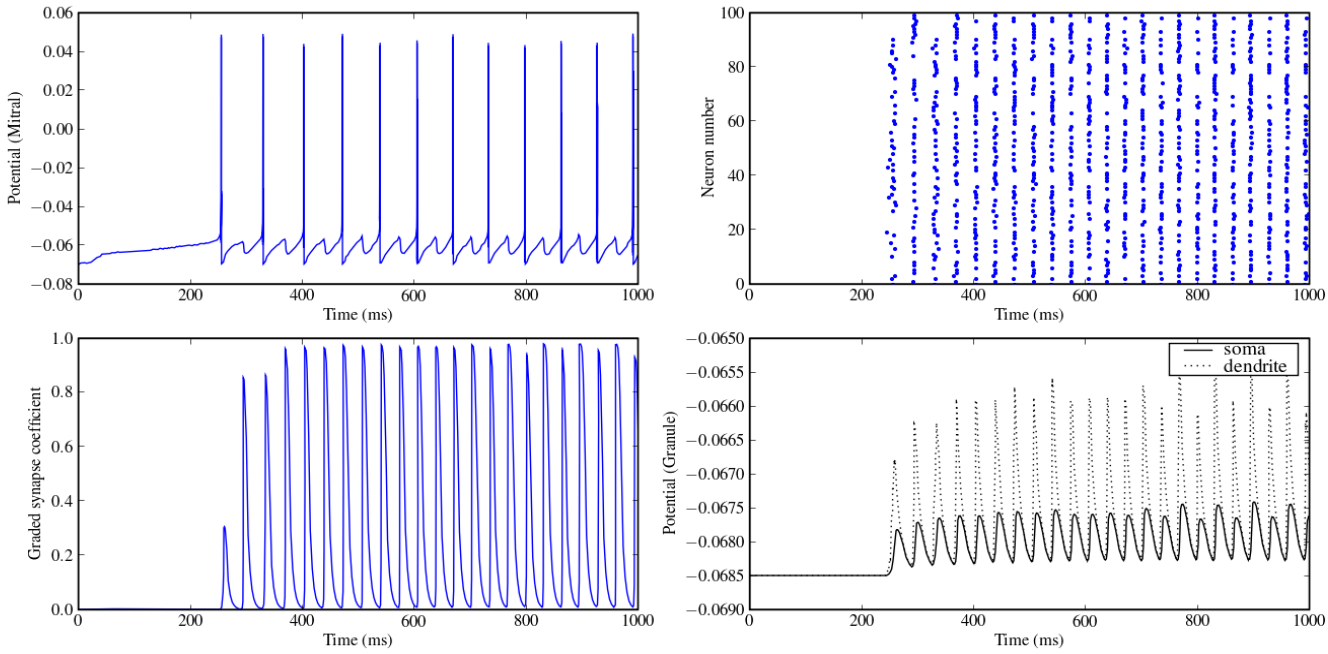

Figure 4. Generation of fast oscillations in a mitral-granule network, controled by subthreshold oscillations. See text for explanation.

In order to test the effect of stimulus intensity on the network oscillation, we varied the intensity of the input current received by the mitral cells, in a range of parameters where mitral cells do not fire on every cycle of the oscillation.

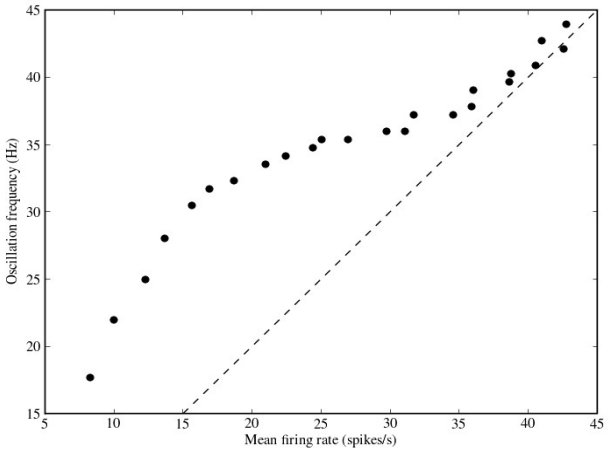

Figure 5. Relation between the oscillation frequency and the population mean firing rate, for different values of the input current.

The results are shown in Figure 5. When the input intensity was increased, the mean firing rates of the mitral cells did increase, almost linearly. However, the frequency of the oscillation frequency changed in a highly nonlinear way. There is range of intensities where the oscillation frequency is much more stable than the firing rate; in this region, a doubling of the firing rate (from 15 to 30 spikes per second) is achieved while the population frequency increases only by 16% (from 31 to 36Hz). In this region, the network responds to an increase of the stimulation intensity mostly by emitting more spikes per cycle, and almost without changing the oscillation frequency. Note that for higher intensities the mean firing rate becomes equal to the oscillation frequency; in this case it is obviously not possible to emit more spike per cycle, and an increase of the input intensity is translated into an increase of the oscillation frequency.

4. Conclusion

Our recording experiments show that increasing the intensity of stimulation results in an increase of the mitral cells firing rate, but leaves the LFP frequency largely unchanged. This suggests that the frequency of the LFP oscillation depends on intrinsic properties of the mitral-granule network. Our computer simulations supports this hypothesis: they show that subthreshold oscillations of the mitral cells can stabilize the frequency of the population oscillation under a wide range of stimulus intensities, despite large changes of the mitral cells firing rates.

The alternance of beta and gamma oscillations in the olfactory bulb during the respiratory cycle remains to be explained. The fact that beta and gamma frequencies do not occur simultaneously suggests that both rhythms might be generated by the same network, operating in two different modes. Previous studies have suggested that the mitral cells show a preferential tuning to either gamma or beta oscillations [8]. Thus, the highly stereotyped nature of both beta and gamma oscillations could result from subthreshold oscillations of these neurons.

Acknowledgements

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