

## Взаимодействие между ультрамедленными флуктуациями нейронных сетей префронтальной коры и колебаниями мозга

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**Целью** нашей работы было изучение влияния различных ритмов головного мозга (тета, бета, гамма ритмы в диапазоне частот от 5 до 80 Гц) на ультрамедленные колебания (с частотой 0.5 Гц и ниже), проявляющиеся в чередовании состояний с высокой и низкой активностью. Эти ультрамедленные колебания обычно наблюдаются при нервной деятельности в человеческом мозге и, в частности, в префронтальной коре во время отдыха. Считается, что они генерируются локальными кортикальными сетями при наличии импульсных входов и нейронного шума. Структура этих колебаний имеет специфическую статистику, а их характеристики связаны с когнитивными способностями, такими как, например, эффективность и емкость рабочей памяти. **Методы.** В нашем исследовании мы использовали ранее построенную математическую модель, описывающую активность кортикальной сети, состоящее из популяций пирамидных клеток и интернейронов. Эта модель была разработана для описания глобального входного воздействия на локальные сети префронтальной коры из других кортикальных областей или подкорковых структур. Динамика модели исследовалась численно. **Результаты.** Мы обнаружили, что увеличение частоты существенно увеличивает время пребывания в состоянии с высокой активностью и, следовательно, повышает устойчивость самоподдерживающейся колебательной активности в гамма-диапазоне. **Обсуждение.** Мы считаем, что такие эффекты были бы полезны для обработки и передачи информации в кортикальных сетях с иерархическим торможением.

*Ключевые слова:* нейронные сети, частотные модели, префронтальная кора, ультрамедленные колебания, ритмы мозга.

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## Interaction between PFC neural networks ultraslow fluctuations and brain oscillations

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**Aim** of the work was to study the influence of different brain rhythms (i.e. theta, beta, gamma ranges with frequencies from 5 to 80 Hz) on the ultraslow oscillations with frequency of 0.5 Hz and below, where high and low activity states alternate. Ultraslow oscillations are usually observed within neural activity in the human brain and in the prefrontal cortex in particular during rest. Ultraslow oscillations are considered to be generated by local cortical circuitry together with pulse-like inputs and neuronal noise. Structure of ultraslow oscillations shows specific statistics and their characteristics has been connected with cognitive abilities, such as working memory performance and capacity. **Methods.** In the study we used previously constructed computational model describing activity of a cortical circuit consisting of the populations of pyramidal cells and interneurons. This model was developed to mimic global input impinging on the local prefrontal cortex circuit from other cortical areas or subcortical structures. The model dynamics was studied numerically. **Results.** We found that frequency increase differentially lengthens the up states and therefore increases stability of self-sustained activity with oscillations in the gamma band. **Discussion.** We argue that such effects would be beneficial to information processing and transfer in cortical networks with hierarchical inhibition.

*Key words:* neuronal networks, rate models, prefrontal cortex, ultraslow oscillations, brain oscillations.

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### Introduction

In the prefrontal cortex a canonical local circuit consists of pyramidal (PYR) neurons coupled together with three types of inhibitory interneurons: parvalbumin (PV), somatostatin (SOM) and vasoactive intestinal polypeptide (VIP) neurons (see schema in Fig. B1). Experimental results showed in simultaneously recorded neural populations of the prefrontal cortex (PFC) superficial layers that activity transits synchronously between high and low activity states lasting several to tens of seconds [1]. This constitutes resting state of activity and has been shown to be important for working memory performance. Interestingly, in the context of low neural firing rates activities, crucial for cellular regeneration mechanisms because of reduced metabolic costs [2], the slower is the switching between high and low activity states, the higher is the rate of information transmission [3]. Therefore, ultraslow activity fluctuations are computationally interesting in the context of quiet wakefulness, notably for efficient detection of important signals in the environment, or for correct transmission of internal signals mediating the consolidation of memories. Furthermore, the mechanisms involved in the generation of ultraslow network activity fluctuations may have important implications for the mechanisms of the generation of persistent activity during working memory tasks and for gating of sensory information

during these tasks. Since specific oscillatory frequency bands modulate brain activity during working memory tasks [4], we tested effects of an oscillatory background on PFC network bistable dynamics in order to study the relative roles of different interneuronal types on persistent activity and gating.

## 1. Methods

In order to better understand mechanisms underlying the changes in endogenous activity under oscillations, we modeled the layer II/III PFC local circuit. PV interneurons, target the axosomatic region of pyramidal cells, exerting divisive effects on their output activities, while SOM interneurons, target the dendrites of pyramidal cells, exerting subtractive type of inhibition by increasing the spiking threshold [5]. VIP interneurons in layers II/III exert inhibitory control of SOM and PV interneurons in the PFC, with a stronger effect on SOM interneurons [6]. Model variables described the firing rates dynamics of various neuronal populations ( $r_{pyr}$ ,  $r_{som}$ ,  $r_{pv}$ , and  $r_{vip}$ ) in a local PFC circuit [7], based on [8] theoretical work for subtractive vs divisive inhibition of pyramidal activity by SOM and PV interneuron populations respectively. We further incorporated subtractive inhibition between SOM, VIP and PV populations [7]. Full model is given by following set of differential equation:

$$\left\{ \begin{array}{l} \tau_s \frac{dr_{pyr}}{dt} = -r_{pyr} + \\ + k_e (\omega_{pyr-pyr} r_{pyr} - r_{pyr}) F_e \left( \frac{\omega_{pyr-pyr} r_{pyr} - \omega_{som-pyr} r_{som} + I_{ext-pyr} - I_{adapt} + I_{oscill}}{1 + \omega_{pv-pyr} r_{pv}} \right) + \sigma_s \xi(t), \\ \tau_s \frac{dr_{pv}}{dt} = -r_{pv} + (k_i - r_{pv}) F_i (\omega_{pyr-pv} r_{pyr} - \omega_{pv-pv} r_{pv} - \omega_{vip-pv} r_{vip} + I_{ext-pv}) + \sigma_s \xi(t), \\ \tau_s \frac{dr_{som}}{dt} = -r_{som} + (k_i - r_{som}) F_i (\omega_{pyr-som} r_{pyr} - \omega_{vip-som} r_{vip} + I_{ext-som}) + \sigma_s \xi(t), \\ \tau_s \frac{dr_{vip}}{dt} = -r_{vip} + (k_i - r_{vip}) F_i (\omega_{pyr-vip} r_{pyr} - \omega_{som-vip} r_{som} + I_{ext-vip}) + \sigma_s \xi(t), \end{array} \right. \quad (1)$$

with  $I_{ext-pyr}$ ,  $I_{ext-pv}$ ,  $I_{ext-som}$ , and  $I_{ext-vip}$  external constant inputs to each neural population type.  $I_{oscill}$  is the sinusoidal component to the external input to PYR population, centered around 0, such that:  $I_{oscill} = I_{max} \sin(2\pi f)$ .  $I_{max}$  is the oscillations amplitude, set at 10% of  $I_{ext-pyr}$ , while  $f$  is the oscillation frequency. We set  $\tau_s = 0.02$  ms, close to each populations' type membrane time constant [9].  $F_e(F_i)$  is a sigmoid response function characteristic of an excitatory (inhibitory) population, which gives a nonlinear relationship between input currents to a population, and its output firing rate.

Parameters  $k_e(k_i)$  modulate the amplitude of firing rate response to input current for pyramidal (inhibitory) neurons. Here  $k_i$  are constants and  $F_e$ ,  $F_i$ ,  $k_e$  we taken as they were developed in [7]:

$$F_{e,i}(x, \theta_{e,i}) = \frac{1}{1 + e^{(x - \theta_{e,i})}}, \quad (2)$$

$$k_e(x) = \frac{e^{(x\theta_e)}}{1 + e^{(x\theta_e)}}. \quad (3)$$

The  $\omega_{x-x}$  (with  $x = pyr, pv$  or  $vip$ ) are the self excitatory (or self inhibitory) synaptic coupling of the excitatory (inhibitory) neural populations. The  $\omega_{x-y}$  (with  $x \neq y$ ,  $x = pyr, pv, som$  or  $vip$  and  $y = pyr, pv, som$  or  $vip$ ) are the excitatory (or inhibitory) synaptic coupling from one population to another. We did not consider self-inhibition in SOM and VIP interneuron populations, since inhibitory chemical synapses between those neurons are rarely observed [9, 10], and did not study PV and SOM direct connections. The parameter  $\sigma_s$  controls the strength of the random fluctuations of neural

populations' firing rate, and  $\xi(t)$  is a white noise process. In simulations we used the Euler method and this terms were produced by appropriate sampling of a normal distribution. In order to model spike frequency adaptation from PYR neurons in the network model, we used the following equation, adapted from [11]:

$$\tau_{\text{adapt}} \frac{dI_{\text{adapt}}}{dt} = -I_{\text{adapt}} + r_{\text{pyr}} J_{\text{adapt}}, \quad (4)$$

where  $\tau_{\text{adapt}}$  and  $J_{\text{adapt}}$  are the adaptation time constant and the adaptation strength of PYR population. We chose  $\tau_{\text{adapt}} = 600$  ms. We used an optimization algorithm, to select parameters ( $\omega x - x$ ,  $\omega x - y$ ,  $J_{\text{adapt}}$  and  $I_{0-x}$ ) reproducing network bistability of pyramidal neurons and interneurons in awake wild-type (WT) mice, with mean activities and durations close to the ones found experimentally. This algorithm created random associations of values between parameters and computed an error for activity properties between simulations and experiments. Details of the methodology are given in [11]. We selected the association of parameter values minimizing the error. The high activity/low activity state durations are computed as for the experimental results (see Methods in [1]).

## 2. Results

We developed a computational model of the local PFC circuit that reproduces the dynamics of resting activity seen in imaging experiments (see Figure 1) in both qualitative appearance of spiking and in statistics of two activity states. This provided a basis for further investigation of the influence of oscillatory inputs on transitions structure of the resting state. The model has following dynamical structure (see [11] for full analysis): there is a bistability between a stable «low activity» where both excitatory and inhibitory neuronal populations are nearly quiescent state and a «high activity state», where both populations produce significant level of activity. Both of these states are nodes. There is a third fixed point of the system that is a saddle. The stable manifold of the saddle form the separatrix between two stable states. For purposes of present study, the system is subjected to an additive noise that produces random transitions between two states. We have previously shown [11] that an appropriate choice of the noise strength can produce transition statistics (frequency and the life-times of two states) that reproduce the experimental data [1]. Figure 1 shows an exemplary experimental data obtained from calcium imaging (panels A1,2,3) using the model structured as shown in panel B1. Panel B3 shows an example of the pyramidal population firing rate dynamics as a function of time. Please note the transitions between two stable states of activity; these transitions are due to additive noise and the transition from the high-to-low states is also partially caused by the adaptation of the PYR firing rate (see equation 2 and the  $I_{\text{adapt}}$  terms in system (1)). In panel B2 we visualize a simulated modulation of spiking in a single pyramidal neuron that is produced by generating spike time using an Poisson process with a time-dependent (instantaneous) rate  $\lambda(t)$  equal to firing rate of the pyramidal population  $r_{\text{pyr}}(t)$  seen in the dynamics of the model (1) as a function of time. We emphasize that the dynamics are generated by the population model and the spike raster is a visualization of spiking of a potential neuron constituent of this population.

We stimulated our optimized model with sinusoid inputs of moderate amplitude and variable frequency. This stimulation was designed to mimic global input impinging on the local PFC circuit from other cortical areas or subcortical structures. We wanted to know how the statistics of the activity states are affected by the sinusoid input. Using computational modeling, we found that externally driven oscillations influence the duration of high and low activity states and that this influence depends on the frequency of the input. In figure 2, we can see that high frequencies (40 Hz, gamma oscillations) increase the durations of both high and low activity states (H-states and L-states, respectively), while low frequencies (5 Hz, theta oscillations) induce shorter H-states and L-states. Furthermore, we notice

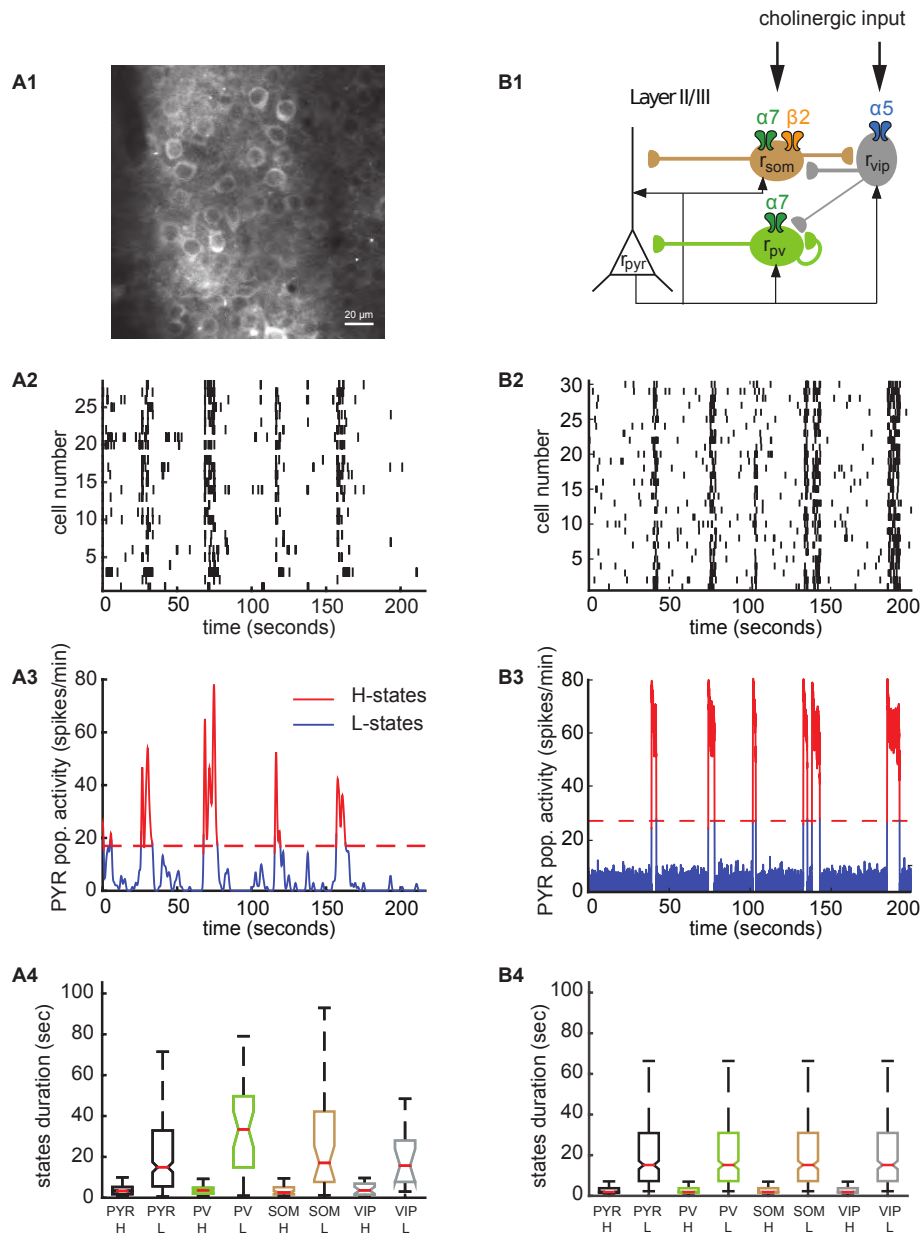


Fig. 1. Bistable firing rate dynamics of interconnected neural populations replicates ultraslow fluctuations recorded in the PFC of WT mice. **(A1)** Two-photon image of *GCaMP6f* expressing neurons, modified with permission from [1]. (Scale bar: 20  $\mu\text{m}$ ). **(A2)** Spike trains of a population of simultaneously recorded cells in a WT mouse, obtained through deconvolution of spontaneous  $\text{Ca}^{2+}$  transients. 80% of the recorded cells are PYR neurons. Modified with permission from [1]. **(A3)** Time varying population mean activity of the neurons shown in A2. The dashed red line delineates the threshold between high and low activity states (H-states and L-states, respectively). Red periods correspond to H-states and blue periods to L-states. Modified with permission from [1]. (See [1] for more info on the methods). **(B1)** Schematic of the studied circuitry. **(B2)** Visualization of single pyramidal neurons activity from the population rate model. To produce this we use the mean population rate produced by the simulated model and creating spike times according to the Poisson process with the rate  $\lambda(t) = \text{mean population rate as a function of time}$ . Note that since this rate fluctuates between the low and high activity states (see panel B3), we see the same in the single cell firing rastergram. **(B3)** Time varying mean population activity of pyramidal neurons, computed from the network model. We use the same method as [1] to delineate H-states (in red) and L-states (in blue)

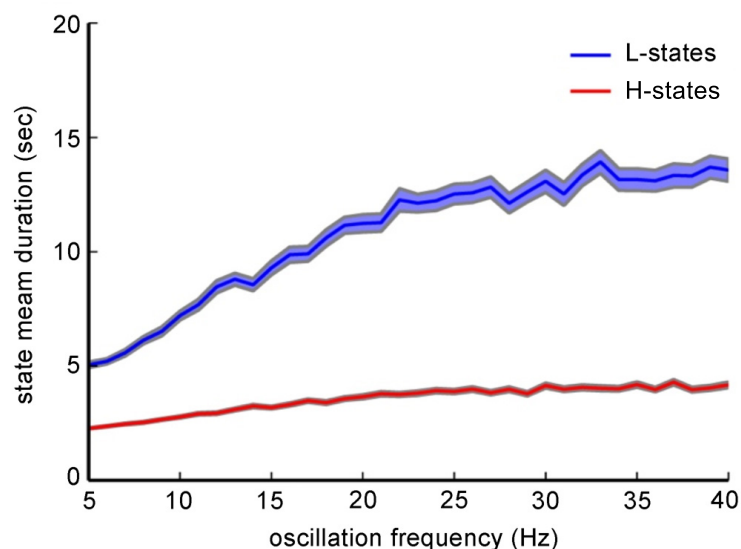


Fig. 2. Active state duration increases with frequency of input oscillations. State mean duration function of oscillation frequency (Hz) of external inputs to PYR population. The blue line shows the evolution of L-state mean durations (sec), while the red line shows H-state mean durations (sec). The shaded areas are  $\pm$  sem

that as frequency increases, the relative effect on the duration of the up-states becomes stronger relative to the duration of the down-states. This means that as input frequency increases into the gamma range, the network becomes more active (mean firing rates increase). During working memory tasks, gamma oscillations correlates positively with memory maintenance, consistent with increased H-state durations found in our results. We further predict higher rates of information transmission associated to gamma bands, since our study associate them with slow switching between high and low activity states.

### 3. Conclusions

In this work we designed a minimal prefrontal cortical circuit model to analyze the dynamics of firing rates of the multiple neuronal population circuit. We developed a dynamical parameter optimization procedure for the circuit model. The optimization allowed us to identify model types that reproduced the experimentally observed data. We previously conducted analysis of the resulting model dynamics and found that the model was bistable with a slow alternation between high and low activity states, just as in the data. We made a stochastic version of the model that with the optimized parameters reproduced the statistics of the experimentally observed upper and lower state durations. We then focused on these statistics and designed oscillatory inputs to the model. Notably we projected the oscillations to the pyramidal neuron population in the model. We then performed analysis of the effects of the oscillation frequency on the state statistics. We found that frequency increase differentially lengthens the up states and therefore increases stability of self-sustained activity with oscillations in the gamma band. We argue that such effects would be beneficial to information processing and transfer in cortical networks with hierarchal inhibition.

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