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Does the phenomenon of stochastic amplification of fluctuations play a relevant role in cortical dynamics?

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Abstract. We review the mechanism of stochastic amplification of fluctuations in the context of fast cortical oscillations observed during up-states both *in vitro* and *in vivo*. For this purpose, we employ minimalistic models based on short-time synaptic depression with or without synaptic facilitation and compare results with empirical observations. The phenomenon of stochastic amplification of fluctuations is shown to be relevant and robust against different regulatory mechanisms and model specificities. In particular, by introducing synaptic facilitation as a possible manner to dynamically tune the synaptic efficacy, we show that, beyond resonancy details, the mechanism responsible for stochastic amplification is robust and persists along a wide range in the synaptic parameters space. In passing, we explain why a similar stochastic amplification cannot possibly be observed in cortical down-states.

Keywords: brain oscillations; Up and Down states; fluctuations; noise induced phenomena; collective behaviour.
PACS: 87.10.Mn, 87.18.Tt, 87.19.L-, 87.19.lc, 87.19.lm, 87.19.ln

INTRODUCTION

Deciphering the diverse patterns of global activity recorded in the brain and associating them with behavioral states are major challenges in Neuroscience [1, 2, 3]. High-frequency neural activity in the β and γ ranges (10 : 100 Hz) has been related to a plethora of cognitive tasks such as working memory [4], selective attention [5], or response to sensory cues [6]; abnormal fast oscillations have been implicated in seizures and pathologies [7]. On the other hand, slow *delta* waves (0.5 : 2 Hz) become preponderant during the deepest stages of sleep, under anesthesia or even during quiet wakefulness [8, 9, 10] and might play an important role in neural plasticity and in the consolidation of new memories [11].

Remarkably, neural activity can be spontaneously generated at the cortical-network level even in the absence of external stimulation. For instance, slow δ waves have been observed both *in vivo* and in slice preparations under different experimental protocols [12, 13, 14, 15] in the form of *up-and-down states* in which a large fraction of neurons alternate between two different stable membrane-potential states: the *down-state* –with a high degree of hyper-polarization and very low activity– and the depolarized *up-state*, with high synaptic and spiking activity[16, 9]. The coherent alternation between such

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two, up and down states gives rise to low frequency δ waves [17] with exciting possible implications [18].

Two interesting empirical observations that we would like to clarify are the following:

- high-frequency oscillations have been observed to occur *within* the active (up) intervals of slow oscillations but not in down states [19, 20, 21]. In particular, the associated up-state power spectra develop a non-trivial peak at some frequency in the β band, between 20 and 30Hz, together with a substantial increase in the spectral power all along the β/γ range [22].
- while global network measurements reveal robust oscillations in the β/γ range in the up-state, individual membrane potentials or synaptic events detected at the intracellular level do not show any trace of oscillations in this range of frequencies.

This suggests, first that oscillations are a collective phenomenon emerging at the network level, and second, that there is no global synchronization locking the rhythms of individual neurons to the systemic one.

Trying to shed light on these issues –and following two recent publications by Wallace et al. [23] and ourselves [24]– we employ minimalistic models able to generate up and down states. As we shall illustrate by working with simple models with short-time synaptic plasticity, the mechanism of stochastic amplification of fluctuations explains in a parsimonious and elegant way all the above-mentioned phenomenology.

STOCHASTIC AMPLIFICATION OF FLUCTUATIONS IN A SIMPLISTIC MODEL FOR UP-AND-DOWN STATES

Minimalistic models for neural dynamics are those in the seminal works of Wilson and Cowan [25] and Amari [26]. These represent the activity of the system through a global (or "mean-field") variable –the population-averaged firing rate– and assume a deterministic evolution for it. Models for network bistability require of some regulatory mechanism such as synaptic depression [27, 28] or a balanced combination of excitatory and inhibitory neurons [29, 30, 31, 32, 33], providing for a negative feedback loop and thus allowing for network self-regulation. These can be easily implemented in simple deterministic models as the above-mentioned ones, allowing for a description of up and down states as corresponding to fixed points of high and low firing-rate, respectively.

Spontaneous transitions between these two deterministic states (i.e. fixed points of the dynamics) can be mimicked by switching-on some stochasticity, able to induce transitions between them. A simple instance of this is the work of Holcman and Tsodyks [27], who introduced a noise source into a simple dynamical model for neural with activity-dependent synaptic plasticity [34]: the noiseless version of the model presents bistability while the noisy version exhibits up-and-down states (see also [35]).

The model of **Markram and Tsodyks** [36, 34] is described by the mean voltage potential, v, and the variable x, which measures the level of available synaptic resources (e.g. neurotransmitters). A dynamical equation for x allows us to model short-time synaptic depression (STSD). The mean voltage grows owing to both external and internal inputs and decreases owing to leakage processes; synaptic resources are consumed in the process of generating internal outputs and spontaneously recover to a target max-

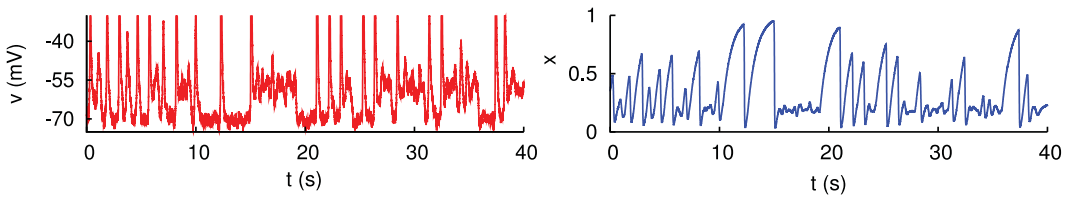

FIGURE 1. Average potential and synaptic utility in computer simulations of the model of Markram and Tsodyks; the system exhibits up and down transitions. In this simulation, noise variances are $\sigma_v = 2.2$ mV/$\sqrt{\tau}$, $\sigma_x = 0$, and time-step 10^{-4} s

imum value, fixed here to $x = 1$:

$$\dot{v} = g_v(v,x) = \frac{1}{\tau}(v_r - v + \omega u x f(v)) \tag{1}$$

$$\dot{x} = g_x(v,x) = \frac{1-x}{\tau_r} - u x f(v), \tag{2}$$

where τ and τ_r are the characteristic times of voltage-leakage and synaptic-recovery, respectively, v_r is the resting potential, ω the amplitude of internal inputs, u the release probability of the neurotransmitters, and –finally– the firing rate function, $f(v)$, is assumed to be of the form $f(v) = \alpha(v - T)$ if $v \geq T$, where T is a threshold value, and $f(v) = 0$ otherwise. Physiologically plausible parameters values are given by $\tau = 0.05$ s, $\tau_r = 0.8$ s, $v_r = -70$ mV, $\omega = 12.6$ mV/Hz, $u = 0.5$, $T = 2.0$ mV, and $\alpha = 1.0$ Hz/mV. For the chosen parameters, there are two stable fixed points (as well as a saddle-point between them). One of them corresponds to a sustained up-state $v^* = v_r + 12.7865$ and $x^* = 0.18817$, and the other to a down-state $v^* = v_r$ and $x^* = 1$ (see Fig. 1). The system experiments a Hopf-bifurcation when decreasing ω, appearing a stable limit cycle with sustained oscillations [27, 37]. This set of equations is deterministic; as in [27], we add noise to have into account some possible stochastic sources (such as irregular external inputs, finite size, or irregular and limited connectivity to name but a few). For simplicity, we add uncorrelated Gaussian white noises $\eta_v(t)$, $\eta_x(t)$ with respective variances σ_v, σ_x, but the forthcoming results do not depend crucially on this choice.

To analyze fluctuations around either of the fixed points, we define $\delta v = v - v^*$ and $\delta x = x - x^*$, and linearize around any of the fixed points:

$$\begin{aligned} \dot{\delta v} &= a_{vv}\delta v + a_{vx}\delta x + \eta_v(t) \\ \dot{\delta x} &= a_{xv}\delta v + a_{xx}\delta x + \eta_x(t), \end{aligned} \tag{3}$$

where $a_{zz'} = \frac{\partial g_z}{\partial z'}(v^*, x^*)$ (z and z' standing for either v or x) are the elements of the Jacobian matrix A evaluated either at the up or the down state. A standard lineal stability analysis of A for the used parameters reveals that the down-state is a node (two real negative eigenvalues) while the up-state is a focus (two complex eigenvalues with negative real part). Defining $\widetilde{z}(\omega) = \mathscr{F}[z(t)]$ as the Fourier transform of either $\delta v(t)$ and $\delta x(t)$, it is straightforward to compute their power spectrum as $P_z(\omega) = \langle |\widetilde{z}(\omega)|^2 \rangle$,

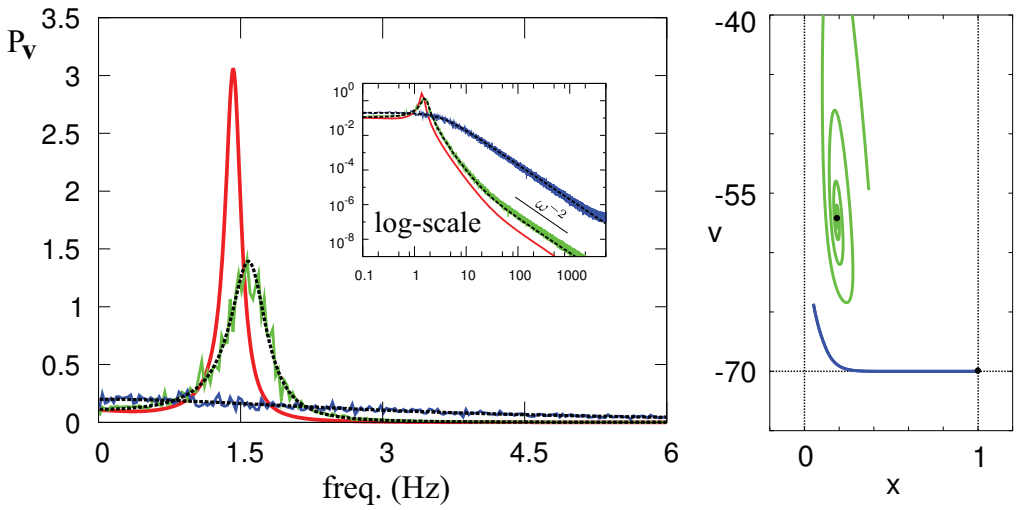

FIGURE 2. Holcman-Tsodyks' model, left: Power spectrum of fluctuations in up- and down-states for average membrane potential v. The main plots show the power-spectra in lineal scale: a marked peak appears for the up-state (green curves) near ≈ 1.5 Hz. Instead, there is no track of similar peaks for down states (blue curves). Observe the excellent agreement between simulation results (noisy curves) and analytical results, Eq. (4) (black dashed lines). Red curve represents the power spectrum for the up-state when synaptic facilitation is incorporated to the model. The peak moves slightly to a lower frequency, and spectrum becomes sharper. The inset represents double-logarithmic plots of the same quantities as in the main plots; in all cases there is a tail w^{-2} revealing the presence of fluctuations at many different scales. All spectra have been generated with $\sigma_z^2 = 0.01 z^*/\tau$, and normalized to unit area. Right: deterministic trajectories for the model without facilitation using different initial conditions. The up-state is a focus (complex eigenvalues), while the down-state is a node (real eigenvalues).

which takes the usual form:

$$P_z(\omega) = \frac{\alpha_z + \sigma_z^2 \omega^2}{\left[\Omega^2 - \omega^2\right]^2 + \Gamma^2 \omega^2} \tag{4}$$

where $\alpha_z = a_{zz'}^2 \sigma_{z'}^2 + a_{z'z'}^2 \sigma_z^2$ and $\sigma_z^2 = \langle \eta_z^2 \rangle$; while $\Omega^2 = \det(A)$ and $\Gamma = \mathrm{Tr}(A)$ do not depend on the noise amplitude. The resulting $P_v(\omega)$ is represented in Fig. 2. Observe that in the limit of small noise amplitude, both spectra exhibit a maximum nearby $\omega = \sqrt{\Omega^2 - \Gamma^2/2}$ (where the denominator of Eq. (4) has a minimum) assuming that the solution of the previous equation exists. Observe the presence of a non-trivial peak for the up-state spectrum, indicating the existence of noise-induced quasi-cycles. This effect, called *stochastic amplification of fluctuations*, has been recently applied in the context of population oscillations in Ecology[38] and other fields such as Epidemiology [39]. It requires the presence of a focus (more specifically, complex eigenvalues with $\mathrm{Im}[\lambda] > \mathrm{Re}[\lambda]$) in the deterministic dynamics plus some additional source of stochasticity. In a nutshell, the gist of the mechanism is as follows: the system tries to relax to the fixed point, but noise "kicks" it away, amplifying some frequencies which are closely related (but not identical) to that of the deterministic damped oscillations. On the other hand, if the system decays towards a deterministic node (i.e. with real eigenvalues), no frequencies are amplified whatsoever (see Fig. 2). This is what happens in

the down-state, where the crossed coupling terms vanish when $f(v) = 0$; accordingly, the derivative of the denominator in Eq. (4) $w^2 = \Omega^2 - \Gamma^2/2 = -(a_{vv}^2 + a_{xx}^2) < 0$ does not vanish for any real value, resulting in the absence of a non-trivial peak in the power-spectrum.

As a second step, we can check the robustness of the mechanism of Stochastic Amplification in the model with synaptic plasticity when we introduce short-term synaptic facilitation. Following Tsodyks and Markram[36], we write a new equation for the release probability of available neurotransmitters, $u = u(t)$ which was taken to be a constant above. Without activity, it recovers to its baseline U_0 with time constant τ_f, while in the presence of activity it increases proportionally to $(1-u)$.

$$\dot{u} = \frac{U_0 - u}{\tau_f} + U_0(1-u)f(v). \tag{5}$$

Fixing $U_0 = 0.05$ and $\tau_f = 1.5$ s, we find that the stable fixed point corresponding to the up-state shifts to $v^* = v_r + 12.5921, x^* = 0.2005, u^* = 0.4708$. On the other hand, the down-state remains at $v^* = v_r, x^* = 1, u^* = U_0$. Computing the power spectrum for each variable we can generalize Eq. 4 to the case with an arbitrary number of coupled equations, obtaining

$$P_z(\omega) = \frac{[\mathrm{Adj}(A - i\omega 1)\langle \vec{\eta}\,\vec{\eta}^t\rangle \mathrm{Adj}(A^t + i\omega 1)]_{zz}}{\det(A^2 + \omega^2 1)} \tag{6}$$

where Adj stands for the adjoint matrix (transpose of the cofactors). In the limit of small noise amplitude, we find a peak at the frequency that minimizes the denominator $\det(A^2 + \omega^2 1)$. Again, a non-trivial peak appears in the spectra only for the up state (at 1.4 Hz), while the distribution becomes sharper even if its structure remains essentially unchanged (see red curve in Fig. 2). Therefore, the mechanism of stochastic amplification of fluctuations described above is robust to the inclusion of synaptic facilitation.

DISCUSSION AND CONCLUSIONS

We have presented a very simple model, including synaptic plasticity as a key ingredient, able to reproduce up and down states. The dynamics is given by two coupled mean-field equations representing the mean activity of the population and the level of synaptic depression (or resources). While the deterministic system presents two attractors, i.e. bi-stability, up and down transitions appear when noise is added to the system.

First, we analyzed the fluctuations around each fixed point by analyzing the power spectrum of fluctuations for each variable. Its structure, or, more precisely, the existence of a peak, depends essentially on the trajectories near the deterministic attractor. If spiral trajectories are present (i.e. focus fixed point) noise may amplify some frequencies in a resonant way, resulting in a pronounced peak in the power spectrum. This can occur in the up-state, where the variables are strongly coupled because of the feedback-loop between excitation and depression. We have verified that the mechanism is robust against the incorporation of synaptic facilitation to the model. Similarly, the same framework

explains why (owing to the effective decoupling of equations) a similar resulting frequency cannot be observe in down states (in accordance with experiments).

These results are in perfect agreement with experimental results (e.g. [22]). However, in order to improve the result for the characteristic frequency a obtain a result closer to empirical values, more detailed models are required. This path has been followed in [24] where –by considering a simple network-version of the model above in which the role of individual neurons can be explicitly followed– we have shown that the peak frequency shifts towards empirically observed values and, more remarkably– that individual neurons follow a rhythm much faster than the emerging collective one, to which they do not lock [22, 24, 23], in excellent agreement with observations.

Summing up, a simple deterministic model able to reproduce up and down states, does also include non-trivial oscillations within the up state but not in the down state when some noise source is switched on. The mechanism of stochastic amplification of fluctuations can explain the structure of the power spectra and other highly non-trivial features of cortical oscillations in a simple, elegant and parsimonious way.

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