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Noise Influence on Correlated Activities in a Modular Neuronal Network: from Synapses to Functional Connectivity

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Abstract. In this work we propose taking noise into account when modeling the neuronal activity in a correlation-based type network. Volume transmission effects on connectivity are considered. As a result, an individual module can be set in an "activated" state via noise produced by the remaining modules. The stochastic approach could provide a new insight into the relation between functional and anatomical connectivity.

1 Introduction

Noise is always present in brain structures in vivo. It stems from several sources, like fluctuation of membrane potential, the very nature of the synaptic input ("synaptic noise"), and the variability of the inter-spike interval in the pattern of activity of a neuron [1].

Experimental and computational studies have demonstrated that noise has an important role in the sensory systems as well as in the cerebral cortex [1,2]. In the latter case, synaptic noise holds the membrane in a high-conductance state, which enhances the computational properties of the network, along with the ability of amplifying weak signals (stochastic resonance) [3] and the capability of detecting coincidences (high-temporal resolution) [1].

Our aim is to study the influence of noise on the correlated activities in a modular neuronal network by using the methods of nonlinear stochastic dynamics. At present, we will focus our attention on the activity of a single module in order to assess how noise produced by the "environment" (the remaining modules) affects its temporal activity profile.

2 Model

In our model the network consists of a series of small-sized modules of high intrinsic connectivity and sparse inter-module connectivity, all together forming a correlation-based type network [4]. For each module it is possible to define an *activity* and a *hard-wired connectivity*. Activity (λ) is simply the fraction of active neurons in the module, whereas the hard-wired connectivity (h=M/N) is the ratio between the

average number of connections of a neuron (M) and the total number of neurons (N) in the module.

Modular neuronal distribution in cerebral structures is allegedly the way brain evolved to ameliorate learning and to adapt to changes. A neural function is assumed to be decomposed in a set of sub-functions each allotted to a specific module. Activities of modules are correlated, thus contributing and integrating each other [5].

Neurons in the modules can communicate among themselves directly through axonal links and action potentials, and/or via volume transmission, i.e., through diffusion of neurotransmitters (NT's) in the extra-cellular space. Such type of communication is possible because part of neurotransmitters spill out of the synaptic gap [6]. These two modes of communication coexist and seem to be both necessary to explain brain functions.

Module dynamics is expected to be complex and highly nonlinear owing to mechanisms which span different spatio-temporal scales. In what follows these mechanisms are discussed based upon experimental results available in the literature. A method is suggested for investigating noise influence on network dynamics.

2.1 Neurotransmitters spillover

Communication among neurons in a network is basically axonal-dendritic via synapses. However, this "hard-wired" type of communication is by no means the only way neurons can communicate. NT's that spill out of the synaptic gaps also contribute to neurocommunication [7]. NT's density in the extracellular space (ECS) increases with the number of active neurons, and it is controlled by diffusion, re-uptake, and enzyme degradation [8]. In the case of glutamate, Rusakov [7,8] found that NT's actually reach post-synaptic (NMDA) receptors in adjacent synapses.

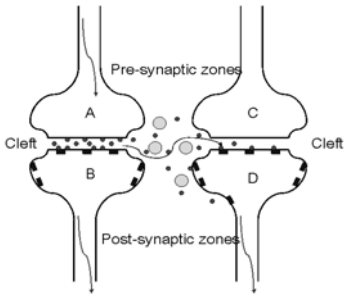

Fig. 1: Arrival of action potential in the pre-synaptic zone (A) culminates in releasing neurotransmitters (small filled dots) in the cleft, thus micro-potentials are generated in the post-synaptic zone (B). Escaped neurotransmitters diffuse in the extra-cellular matrix (gray dots) reaching post-synaptic receptors (small filled rectangles) in the adjacent post-synaptic zone (D): new micro-potential are generated by means of diffusion.

In the hippocampus, about 30% of NMDA receptors of a single synapse is activated by action of external glutamate. Thus, given sufficient activity, action potentials can be generated by NT's spillover, which is a less expensive way of communication (see Fig.1). In contrast, glutamate spillover from pyramidal neurons can reach

interneuron's synapses where it can activate MG (metabotropic glutamate) receptors, which, in turn, enhances releasing of GABA, an inhibitory neurotransmitter. Thus, glutamate spillover is self contained through a feedback inhibitory effect [9].

2.2 Functional hard-wired connectivity

Diffusive neurotransmission due to NT's spillover competes with hard-wired connectivity. When λ is low (Fig. 2, a), the density of neurotransmitters in the extracellular space is proportionally low, thus spillover effects are negligible. In this case, signaling essentially relies upon action potentials (AP) running along the links, which implies considerable amounts of metabolic energy (ATPs) for sustaining AP transmission as well as vesicle recycling [4]. As λ increases (Fig. 2, b), NT's build up, thus diffusion mode prevails over, and partly replaces hard-wired communication, with less energy involved. Thus, only part of the M links are sufficient, the remaining ones (gray links in Fig. 2, b) being replaced by volume transmission. Beyond a certain level of activity spillover inhibitory effects (as in the case of hippocampal glutamate) cooperate to reduce the activity by cutting out ("killing") more hard links from the communication process. As a consequence, only M^* of the M links are actually sufficient (active), the remaining M-M^* being inactive (gray links). Thereafter, NT's re-uptaking and degradation reduce NT's concentration thus reviving hard-wired mode.

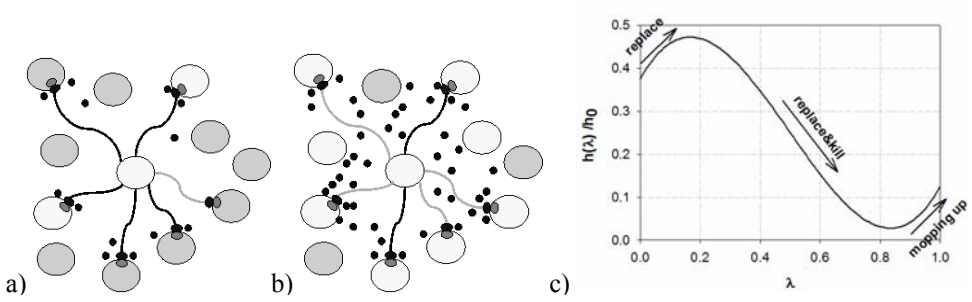

Fig. 2: (a) A few neurons are active (white circles): most links of an active neuron (central neuron) support action potentials; (b) most neurons are active: the extra-cellular NT's concentration is high. An active neuron presents only few active links since most are replaced by diffusion; (c) in the initial phase ($\lambda \leq 0.15$) diffusive mode gradually replaces hard-wired mode. In the following descending phase ($0.15 < \lambda \leq 0.85$) hard links are not only replaced by diffusion but they also are cut off by GABA inhibition: two synergic effects ("replace-and-kill") concur towards reduction of the number of active links. In the last phase, neurotransmitters are "mopped up" through re-uptake and/or eliminated by enzyme degradation, thus reducing the influence of diffusion-mode.

Spillover effects upon connectivity are taken into account by defining a "functional" hard-wired connectivity which depends on the level of extra-cellular NT's concentration, or, equivalently, on λ . Thus, we have:

$$h(\lambda) = M^*(\lambda) / N \qquad (1)$$

where $M^*(\lambda)$ is the number of active links per neuron for a given NT's concentration. The simplest power-law for $h(\lambda)$, which better describe how M^* would vary with λ (see Fig. 2, c), is a 3rd order one, i.e. :

$$h(\lambda) = h_0\left[a\left(\lambda-\lambda_0\right)^3 + c\left(\lambda-\lambda_0\right)+d\right] \quad (2)$$

where h_0 is the hard-wired connectivity, and a, c, d and λ_0 are appropriate parameters. A gradual transition from hard-wired to diffusive modes may be relevant for stabilizing cell-assembly activity, and the theta rhythmic bursting activity involved in the hippocampal learning-memory functions [10].

2.3 Metabolic profile of a single modular neuronal network

The metabolic cost for driving a single module of N_0 neurons is written [4] as :

$$C = N_0^2 h_0\left[\alpha\lambda^2 + \beta\lambda\right] \quad (3)$$

where h_0 is the hard-wired connectivity, and α and β specific cost coefficients. Replacing h_0 with $h(\lambda)$ in Eq. 3, the expression for the metabolic cost becomes a 5th order power law in λ. For similar results see Hopfield network [11]. Fig. 3 (left) shows the metabolic profile vs. λ in the range of meaningful values (λ=0,1). We assume C in Eq. 3 as a generalized potential [4]. Thus, if initially λ<0.4, in absence of any external input, the activity goes to zero. For λ>0.4 the activity stabilizes at λ=0.8, i.e., at the minimum of potential energy.

2.4 Single-module stochastic dynamics

In order to assess how environmental noise influences the temporal activity profile of a module, we interpret the dynamics of $\lambda(t)$ as the motion of a fictitious Brownian particle subjected to a potential like shown in Fig. 3 (left) [12]. The corresponding law of motion, in overdamped regime, is a Langevin equation [13], i.e.:

$$\frac{d\lambda}{dt} = -\frac{dC}{d\lambda} + \sqrt{\varepsilon}\,\xi(t) + A_0\cos\omega t \quad (4)$$

where ε is the intensity of a white Gaussian noise $\xi(t)$, with the following statistical properties:

$$\left\langle \xi(t) \right\rangle = 0\ ; \quad \left\langle \xi(t)\xi(t') \right\rangle = \delta(t-t') \quad (5)$$

with $\delta(t)$ the delta function. The overdamped regime is justified by the strong dissipative character of biological neural structures. In Eq. 4, $-dC/d\lambda$ is the driving force acting on the system, and $A_0\cos\omega t$ an external periodic force.

3 Results: Noise-induced temporary module activation

Noise produced by the remaining modules can actually play a role in driving the system towards the minimum of potential energy (λ=0.85 in Fig.3, left). In absence of noise (deterministic case), with initial values λ_{ini}<0.4, the particle never enters the potential well, and returns to λ = 0 (absorbing barrier) in a time τ (*escape time*) that

depends on λ_{ini}. In presence of noise (stochastic case) and for identical initial conditions, the system can enter the potential well, remaining trapped for a while, and then escape reaching the threshold at $\lambda = 0$. In this case, τ becomes stochastic and increases considerably. In order to calculate τ in the metastable state we solve Eq.4, by numerical simulations in absence of external periodic force. We consider the mean escape time (MET) obtained by solving Eq.4 iteratively and averaging over N realizations. In our simulations MET is calculated for different initial values, λ_{ini}, (see Fig.3, left) and several noise intensities ε. The number of realizations is $N=10^4$. The results are shown in Fig.3 (right).

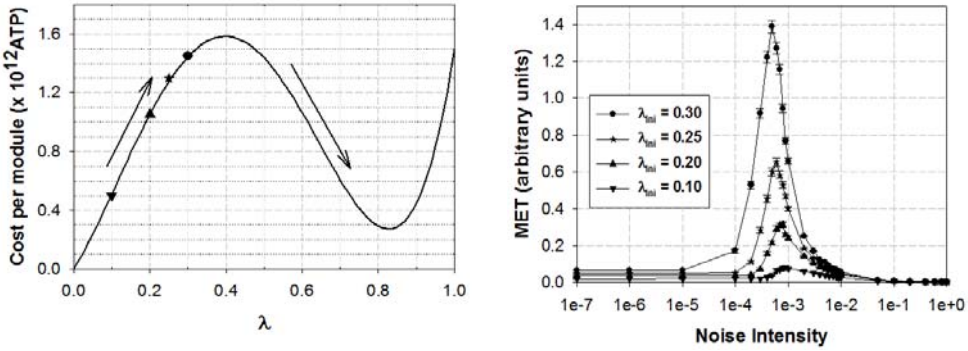

Fig.3. *Left*: Potential energy (C) of the system vs. activity. The force $-dC/d\lambda$ drives the activity of the module in the range (0,1). *Right*: Mean escape time τ vs. noise. For low noise intensity ($\varepsilon<10^{-5}$), $\tau\approx0$: the activity quickly drifts to zero. For noise in the interval 10^{-4},10^{-2}, τ exhibits a non monotonic behavior with a peak, whose value increases as λ_{ini} approaches 0.4 (*left*). For higher noise intensities ($\varepsilon>10^{-2}$) the system quickly leaves the metastable state ($\tau\approx0$).

From Fig.3 it is evident how appropriate levels of noise may cause module activation and allow the system to stay longer in the metastable state with the least consumption of metabolic energy. These features are compatible with a scenario where ATP′s resources are limited although renewable, and also account for spatio-temporal patterns of activity observed in the brain.

4 Perspectives: Application to functional neuro-imaging

An important question is how to relate functional connectivity to anatomical connectivity [14]. This is a central issue related to the more general *form-function* problem in the brain. Functional connectivity, resulting from time-correlations of activities of separate brain regions, is actually measured through functional neuro-imaging based on hemodynamic (fMRI, PET) or magneto-electric methods (EEG), yielding "functional connectivity maps" (*functional networks*). Unlike functional

connectivity, our proposed "functional hard-wired" connectivity is based on the actual anatomy, upon which a mechanism of selection of the links is superimposed. Thus, only *active* links are involved in the measured correlations. Experimental results obtained using hemodynamic-based methods could then be compared with our computer simulations, hopefully casting new light on the relation between functional and anatomical connectivities.

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