Complex Spiking Behavior from Noise-Driven Neuron Interaction

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Abstract. A model of noise-driven biological neocortical networks which is based directly on rat neocortical *in vitro* recordings is introduced. Assuming only binary interaction, the model shows how complex spiking behavior is generated through the noise and gives a full description of the emerging spiking patterns. Mathematical universality properties predict that these patterns are independent of the individual neurons. These properties furthermore imply the observability of these patterns in *in vivo* neocortical networks, in the form of a complex background activity on top of which the processing of "real" data is performed. Interspike interval histograms are derived from this model and compared with the corresponding experimental histograms. Considerable agreement is found, which is notably expressed by the fact that both distributions are long-tailed.

1 Introduction

Neocortical circuits are formed of recurrently connected neurons. These neurons are of two basic types, inhibitory and excitatory, which are reciprocally coupled in monosynaptic or polysynaptic arcs. The possible roles of these connections have been the subject of many experimental and theoretical analyses. Little attention has been given to the effect of recurrent coupling on the global patterns of activity generated in extended recurrent circuits of spiking neurons. Preliminary evidence from combined optical and single unit recordings in the primate visual cortex indicate that single unit responses occur within complex global patterns of activity [1]. However, the nature of this activity in large populations of neurons is not well understood.

The suggestion that cortical networks may become chaotic in some circumstances [2] is particularly interesting in view of our recent demonstration that when recurrent excitatory-inhibitory connections are activated experimentally, individual neurons exhibit both regular and chaotic firing patterns [3]. In these experiments, regularly firing cortical neurons recorded *in vitro* exhibit chaotic firing patterns when inhibitory pulses are applied with a particular frequency relationship to the regularly firing neuron. In this contribution I show how a simplifying limit of the network interaction yields analytical results and mathematically safe statements about the complexity and stability of spiking patterns in neocortical networks.

2   Noise-driven neocortical interaction

The noise-driven model of neocortical interaction that I am proposing is based on experimentally measured neuronal behavior. Neurons in the cortex receive input from other neurons and, when the firing threshold is reached, fire an action potential (the "spike"). Although synaptic output is released in quantals, neurons receive inputs of different orders of magnitude:

- Small-scale noisy input (e.g., from remote synapses) drives the neuron towards regular spiking with well-defined periodicity
- Strong input from next neighbors (neurons or a group of synchronized neurons) arrives at the neuron as a simple, ideally periodic, structure in time
- Medium-size interactions that may reflect specific conditions in the neighborhood of the neuron

Due to the enormous number of synaptic contacts, a large number of small-scale synaptic inputs can be expected to arrive at the neuron [4]. Assuming a Gaussian central limit theorem behavior of the arriving input, the neuron receives an almost constant inflow of charge that can be represented by a constant driving current. This point of view is in accordance with the mathematical idealization made in the cable model of the neuron [5], where the random walk aspects, generated by the random arrival of excitatory and inhibitory input, are completely neglected and the regular spiking neuron is described by a limit cycle solution of the associated oscillator equations. In addition to the small-scale noise, information from other neurons arrives in the form of substantial packages of spikes, received within a certain small time interval. In my model, the level of noise together with strong synaptic inputs carry the information to be processed in the neocortex. In the mathematical description, strong inhibitory or strong excitatory synaptic inputs correspond to a perturbation of the limit cycle solution. This configuration is the starting point for our approach that is directly based on experimental measurements. It allows the complete determination of the spiking patterns that emerge under strong binary synaptic interaction.

In our experiments with real neurons, slices of rat neocortex were prepared for *in vitro* recording. Following standard techniques, individual pyramidal neurons in layer 5 of barrel cortex were intracellularly recorded with sharp electrodes. To induce regular firing, a constant current was injected into the neurons [4,6-7] The regular firing neuron was periodically perturbed by a strong extracellular stimulation of a synaptic input to the neuron. Excitatory perturbations were generated by the stimulation of adjacent white or gray matter by means of bipolar electrodes, inhibitory perturbations were generated when fast excitatory transmission was blocked pharmacologically by application of DNQX and AP5 while regular current pulses were applied to a fiber making a synaptic contact with the regularly firing neuron. In the

context of *in vivo* neural networks, these perturbation paradigms can be regarded as representations of synaptic input from strong synaptic connections, see, e.g., Ref. [6]. Reyes & Fetz (1993) describe in detail similar experiments. In fact, our approach can be seen as an extension of their work.

To investigate the effect by perturbation to the limit cycle, the techniques originally put forward by Glass and Mackey [7] are useful. Of interest is the typical response of an intrinsically regularly spiking neuron to synaptic perturbation of another regularly spiking neuron. Measurements reveal that the response of the targeted neuron has strongly nonlinear characteristics [8]. At fixed perturbation strength, the effect of the perturbation depends on the *phase* ϕ (with respect to the neuron's own regular spiking) at which the perturbation is applied. This property is captured by the *phase response function* $g(\phi)$, which returns the quotient between the perturbed interspike interval length to the intrinsic (i.e., unperturbed) interval length as a function of ϕ. The phase response function g is obtained from a suitable fit through the experimental data points. The phase response and phase return function are related through

$$f_\Omega : \phi_2 = \phi_1 + \Omega - g(\phi) \ (\mathrm{mod}\,1), \qquad (1)$$

where the parameter Ω is the quotient of the intrinsic interspike time T_0 of the targeted neuron divided by the interspike time T_s of the targeting neuron [7].

On the basis of experimental results, we are able to explicitly include the dependence of the phase response function on the stimulation strength K [8]. This functional dependence has the form

$$g_{\Omega,K}(\phi) = g_{\Omega,K_o}(\phi - 1)K + 1. \qquad (2)$$

The involved reference curve g_{Ω,K_o} was measured at 75% of the maximal perturbation of the curve. The physical stimulation strength was, to reasonable accuracy, proportional to the perturbation of g, expressed by means of K. Investigation of the returned periodicities as a function of Ω, K results in typical Arnol'd tongue structures [9], see Fig. 1. For each periodicity p, there are different Arnol'd tongues which comprise areas in the Ω, K parameter space having solutions of the same periodicity p. Note that all periodicities appear, according to the Farey-tree, but with ever smaller basins of attraction. For the different areas, the stability properties of the solutions, which can be measured by the Lyapunov exponent $\lambda_{\Omega,K}$ [9], are of interest. Zooming in on the Arnol'd tongues reveals that for inhibition, chaotic behavior is possible ($\lambda_{\Omega,K} > 0$), at least from the numerical point of view. However, large input strengths are needed to generate this response. Analytic investigations prove that chaotic behavior indeed occurs on a nonzero set in the relevant parameter space [8]. Excitatory stimulations always yield invertible phase return maps on the biologically meaningful parameter space and, as noninvertibility is required for chaotic response, fail to produce chaotic behavior.
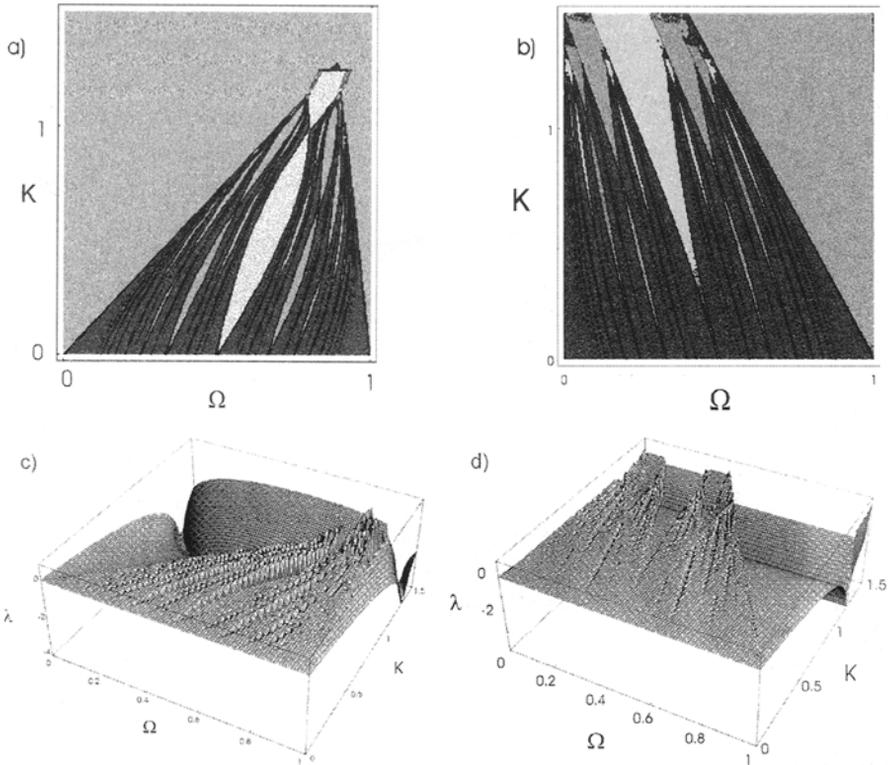
Fig. 1. Topological response of perturbed neurons, for perturbation strength K. Gray levels indicate the value of the periodicity $p \in \{1, .., 9, \geq 10\}$. Largest areas correspond to $p = 1$ (dark gray) and $p = 2$ (light gray), a) inhibitory, b) excitatory case. Stability of neuron response to perturbation measured by Lyapunov exponents: c) inhibitory, d) excitatory case. Chaos is possible above $K \sim 0.95$, but only for inhibition.

3   Towards realistic biological networks

Since the approach is directly based on biological measurements, the question is relevant how much the obtained results depend on experimental variability and on the choice of the fit to the experimental data points. The appropriate mathematical question is answered by the circle-map class property [10]. If f_Ω is varied, but still continues to belong to the circle-map class, then the universality principles of this class imply that all qualitative results remain unaffected, where "qualitative" comprises all topological properties of the results, e.g., the structure of periods. However, metric properties, for example, may differ. Fortunately, the criteria for belonging to the circle-map class are of a general nature, enclosing, e.g., piecewise linear approximations to the data points as well as (bad) polynomial fits. Surprisingly, the very strong universal-

ity features of the circle map class imply that very accurate measurements of phase response functions do not contribute as much to the understanding of the spiking mechanism as might be expected (However, as a possible benefit, a comparison between phase response functions from biophysical simulations and from experimental measurements can determine with accuracy some of the various simulation parameters that are otherwise inaccessible).

In realistic cortical networks, the ideal conditions for observing the predicted spiking behavior are as follows:

- no change in the intrinsic firing rate or in the excitability of the neurons
- sufficiently stable limit cycle behavior
- fast (exponential) decay of interaction between the neurons as a function of nearest-neighboring order

The last property should restrict strong interaction to nearest neighbors. Notably, information can only be encoded in terms of phases, not firing rates, under these ideal conditions. Real networks, however, are not ideal. Consider how critical the above-mentioned assumptions are in the case of real networks. The implications by the first condition for the processing of neocortical information will be discussed at the end of this paper. For the statements on continued perturbations it is essential that the neuron is completely reset after firing. This required stability of the limit cycle can be checked by comparing model predictions to experimental results. In continued perturbations of the rat neurons, periodic spiking behavior up to period 8 was found, at the predicted values of Ω for intermediate stimulation strength [11]. This shows that the required stability property is satisfied with good accuracy. Higher periods have small basins of attraction that are unresolvable due to the experimental noise. Whereas our experimental pulse-perturbations show traces of the experimental noise, the nonlinear dynamics approach is able to describe the noise-free situation! The strength of the experimental noise can be estimated by adding Gaussian colored noise to Eq. 1. A smearing of the bifurcation structure that is monotonic with the strength of the added noise is observed. This effect is in excellent agreement with the results on experimental continued perturbations when the noise level is about 5% of the signal. Because safe mathematical grounds exist to ensure qualitatively similar characteristics for ternary and higher interactions [12], our most critical assumption is the separation of scales of the input as a function of the next-neighboring order. Such a separation is generated by the different types of synaptic input in a network (-strong input, caused by the strongest connected next-neighbor neuron or by a group of synchronized neurons; -medium size input of longer periodicity or of chaotic nature; -small-scale, diffuse, decorrelated input, obeying the Gaussian law of large numbers). Expressed in terms of the maximally applicable experimental stimulation strength (i.e., $4/3K_0$), we estimate these inputs to be of the order $10^{-1}, 10^{-2}$ and 10^{-4}, respectively, which would be consistent with our theoretical approach. Unfortunately, little is known about the goodness of this separation of scales in real networks.

The effect of a medium-size perturbations on the binary interactions can again be estimated by numerical simulations. To this end, Eq. 1 is generalized to $f_{\Omega,K,\hat{K}} : \phi_{n+1} = \phi_n + \Omega - K(g(\phi_n) - 1) + 1 - \hat{K}\sin(\omega_n)$, with $\omega_{n+1} = \omega_n + \omega_0$, where $\omega_0 = 0.1$ and $\hat{K} = 0.05$ are fixed. In this way, the strength $\hat{K}$ of the secondary perturbation was of the order of 10% of the average of K, and orbit points were identified if they differed by less than 10^{-2}. Again, the Arnol'd tongue structures were calculated; the results imply that our approach indeed may provide a good approximation to real cortical networks.

As a result, the following behavior of real noise-driven cortical networks is suggested: locally, low-periodic spiking behavior may be expected in abundance, by the interaction of otherwise freely spiking neurons. This periodic response is organized along Arnol'd tongues and obeys the circle-map class universality. As a consequence, the network is able to respond locally with any desired periodicity. While for weak local interaction the local spiking behavior is dominated by a wealth of different periodicities, for stronger interaction, there is a tendency for the response to settle towards more simple and more stable spiking patterns. These spiking patterns are in sharp contrast to the chaotic response which exists for strong inhibition on a nonzero Lebesque measure of the parameter space. This means that chaos should be observable, or that systems could be tuned to this state. However, it is noteworthy that chaos requires comparatively strong strengths of stimulation and only occupies a small portion of the parameter space. Using the universality principles of the circle-map class, we are able to prove that our experimental observations do not depend on artificial preparation, but are "generic" for our set-up. We propose that in less ideal networks the described behavior plays a role similar to the unstable periodic orbits in chaotic systems. They provide the backbone for the complex structure hidden in the seemingly intractable chaotic motion.

From an information-theoretic point of view, the emergence of stable periodic firing patterns of all periods is a remarkable property of the perturbed neuron. The usual chaos control paradigm for the transmission of information [13] starts from a chaotic ground state and then applies control techniques to arrive at a desired periodicity. The symbol to be transmitted is then encoded in terms of this periodicity, similar to the encoding by the ASCII table. In our case, both excitation and inhibition, can perform the same task with ease, simply through a variation of the frequency or the stimulation strength of the sender, or by adjustment of the excitability of the receiver. In this interpretation, changes in the firing patterns which only affect the value of Ω can be interpreted as rate-coding mechanisms, while changes mainly into the direction of K can be seen as synchronization effects.

4   Long-tailed interspike interval histograms

Experimentally, network interactions are mostly studied by looking at individual neuron interspike interval distributions. A common belief is that these distributions are approximately Gaussian or Poissonian. I believe that models of long-tailed distributions are more appropriate. The reasons for this belief come from measured interspike distributions of *in vivo* experiments, and from models based on *in vitro* experiments. Our next aim is to mimic the interaction with the quasistatic next-neighboring neuron and also to include dynamic interactions. We therefore perform an average over the Arnol'd tongue structure, with respect to the Lebesgue measure in the relevant region of the K, Ω-space. We start with a unit interval and perturb it by a random number of randomly excitatory or inhibitory perturbations of different strengths. From this process, analogous to the experimental set-up, an interspike interval distribution is generated. A typical result is shown in Fig. 2 (left) in comparison to the experimental result (right). As can be inferred from this figure, almost perfect long-tail behavior is displayed in both cases, along with a behavior towards zero that can be expected from the theory of random processes. The histograms show Lévy-type behavior [14], with a power-law exponent of $\alpha \approx 1.8$. The histogram from simulations was obtained by restricting excitabilities to a range of strengths $K \in [0.005, 0.255]$, measured in units of the maximally applicable perturbation strength. These values of K are biologically reasonable and significant for close-to- equilibrium states of the brain. Choosing higher ranges of excitabilities yields less evident Lévy behavior. This is partly due to the appearance of a phenomenon which is widely known to the experimentalists as the "second frequency'", a phenomenon that consists of an additional wiggle in the interspike interval density, obstructing the formation of a clean power-law decay. In our approach, these wiggles emerge in a systematic way, and a large (in principle, infinite) number of such high order frequencies should be observable, given a sufficient resolution of the data. In this way, they are characteristic for a fractal aspect of the measured interspike signal that has earlier been claimed by Teich [15].

5   Phase-coupling mechanisms

Synchronization is an important effect in cortical function, especially in connection with feature binding. Unfortunately, synchronization beyond binary interaction is not possible in the presented model. However, synchronization is known to be a prominent feature of coupled map lattices. In biological neocortical networks, phase-coupling can be thought to be realized by electrotonic coupling or transmitter spill. I want to explore the view that a lattice [16-17] of binary interactions on which medium-size input is represented by diffusive coupling [17], is the appropriate description. In this refined model of
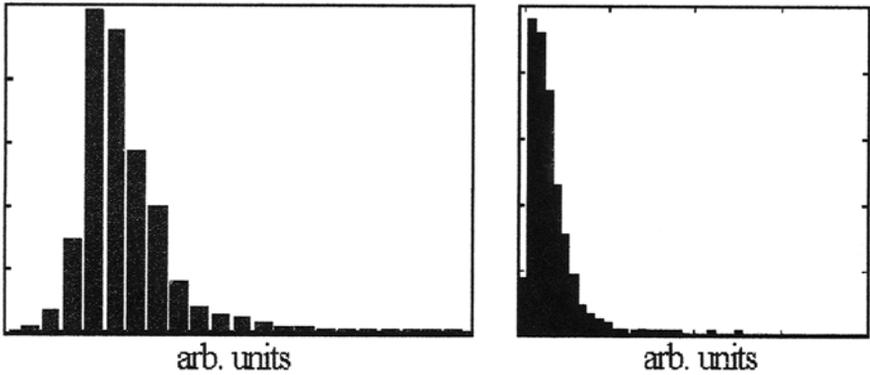
Fig. 2. Long-tailed interspike interval histograms. Left: from the theoretical model. Right: from a complex-type neuron in cat striate cortex. This histogram contains the neuron's combined responses to five, 4 sec. presentations of a spatiotemporally optimized sine wave grating at 40% contrast.

neocortical interaction, the coupling strengths are chosen at random under the constraint of a given overall coupling strength k_2. As synchronization can be associated with characteristic returning phase patterns, the site-averaged difference δ between an initial configuration of the network and its nearest return after a given evolution time should provide an approximate measure of synchronization. Simulation results of the refined model clearly show that inhibition, compared to excitation, has a tendency towards synchronization. Fig. 3a displays these findings as a function of the different network parameters. If inhibition can generally be associated with stronger synaptic inputs than excitation, this may provide a partial, though not conclusive explanation of our findings. Fig. 3b also shows the dependence of δ as a function of the coupling strength k_2. Observed that around $k_2 \sim 1$, the network behavior changes from local chaos to global chaos of "turbulent" characteristics, along a paradigm that is well- understood. The "turbulent" behavior is similar to the "synchronized chaos" observed by Hensel and Sompolinski [18]. The Lyapunov exponents of the network corroborate these findings. As soon as the phase-coupling interaction is turned on, instability is imported into the system that can only be controlled for $k_2 \sim 1$. Around this working condition, the network could be synchronized by pure phase-coupling mechanisms. Conceivably, recurrent inhibitory connections in biological cortical networks are efficient enough to establish such conditions. In order to control wide areas of synchrony, however, it may be more efficient to globally modulate the activity of the involved neurons.
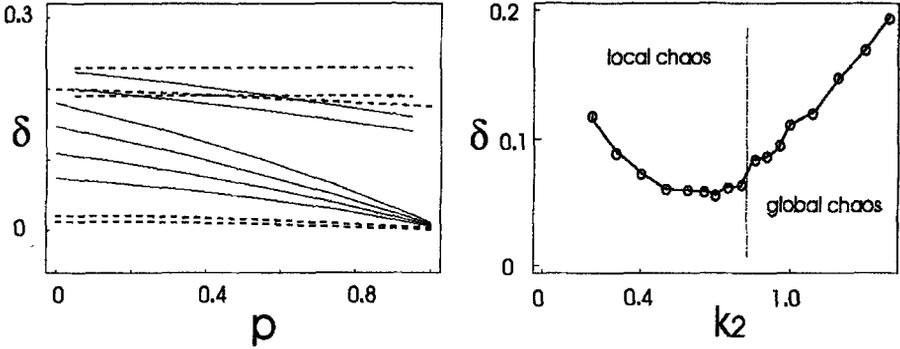
Fig. 3. Left: Pattern deviation per site δ as a function of K, k_2 and percentage P of inhibitory connections. From top: Dashed lines: $\bar{K} = 0.05$ (too low), $k_2 = 0.1, 0.2$, and $\bar{K} = 0.55$, $k_2 = 0$. Full lines: $\bar{K} = 0.15$, $k_2 = 0.1, 0.2$; and $\bar{K} = 0.55$, $k_2 = 0.1, 0.2, 0.4, 0.8$. Bottom, dashed: $\bar{K} = 1.15$, $k_2 = 0.1, 0.2$.
Right: δ as a function of k_2 for $P = 0.2$. Beyond $k_2 \sim 1$, the characteristics change from local chaos to global, turbulent, chaos.

6   Information-processing features

If we insist on the constraint of fixed excitabilities of the individual neurons, the network nevertheless may be able to process information. In a refined model of phase-coupling, a learning-type algorithm is applied to the connection strengths between lattice sites. Those connections which are in phase are increased in strength, while out-of-phase connections are suppressed. Simulations of this model show a quick convergence towards stabilized connection strengths, within a few steps of iteration. Surprisingly, it is seen that different border patterns induce very localized changes in the phase pattern of the more central parts of the network. The locations of the affected lattice sites (called "coding sites") are specific to the applied patterns. More similar border patterns trigger more similar patterns of coding sites. These results suggests that the described paradigm could be a very efficient way of processing neural information. Although such computational processing may be difficult to detect in real neocortical networks, the observation seems worthy of further investigations.

7   Conclusion

Simple principles (binary interactions and phase-coupling) may be responsible for periodic and aperiodic spiking behavior in biological neural networks. For binary neuron interaction, topological and metric properties of the emerging spiking behavior have been formulated in terms of mathematical existence and uniqueness theorems. In the regime where the neural network activity is

dominated by noise and binary next-neighboring neuron interaction, this led to a full explanation of experimentally observed spiking behavior of neurons. Moreover, under these conditions a quantitative description of the natural abundance of the different periodic spiking patterns and of their stability properties can be given. Simulations and theory show that this quantitative description is valid for binary neuron interaction in a generic way.

My model shows how binary neuron interaction may emerge locally within more general noisy neocortical networks. My numerical evidence indicates that the influence of medium-size input may be treated as a perturbation of dominant binary neuron couplings. This evidence allows the conclusion that the patterns generated by binary interaction should be observable during *in vivo* experiments of the neocortex, as relatively simple subsystems embedded in the whole network. Moreover, this observation also led to a straightforward explanation of particularities of experimental *in vivo* interspike interval distributions. In the future, our insight into the generic effects exhibited by periodically perturbed regularly spiking cortical cells could be essential for hardware implementations of cortical cell response. For a successful implementation, it will be important to better understand how "real" data is processed on top of the complex activity that we have shown to emerge in simple noise-driven networks. More experiments on real and experimental noise-driven neural networks are needed to understand this important aspect of neocortical network processing.

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