Cortical correlated spiking activity: from networks to neurons.

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Abstract

In this thesis we have studied the statistical properties of the inputs to a cortical neuron at the millisecond time scale, neuronal signal transduction properties, and the implication of the results in terms of coding mechanisms. We questioned what the correlation properties of the afferent inputs to a cortical neuron are, and how they affect the cellular response properties in the supra- and sub-threshold domains.

It is currently not possible to use a direct experimental approach to study the spiking activity of very large ensembles of cells. To measure the activity of a population of input cells to a target neuron with good spatial (micrometer) and temporal (millisecond) resolution, it would be necessary to record from several thousands of cells at the same time, with microelectrodes inserted in the cortex. The current limit for this technique is of a few hundred cells, at most. Thus, we did not perform experiments as such, but used a theoretical approach based on Combinatorics, Design Theory, and numerical simulations. In the first part of this study (Chapter 1 and 2), we used available physiological data about single cells and pairs of cells activity, to characterize the dynamics of several thousands of neurons. The physiological data considered relates to the high variability observed in the neuronal spike timing, and to the correlation properties of pairs of neurons in the sub- and supra-threshold domain. These three experimental evidences are used, within a statistical framework, as dynamical constraints to limit the possible dynamical states available for the collective dynamics of large ensembles of cells. The results prove that whenever the three constraints are satisfied, unitary events emerge in the ensemble dynamics. Given the broad scope of such constraints, we conclude that unitary events are a natural phenomenon of the cortical dynamics.

Following this result, we examined the impact of such network dynamics on the response properties of a single cortical neuron. We adopted two different approaches (Chapter 3 and 4, respectively).

1) We used computer simulations to study the impact of unitary events in the afferent network to a detailed compartmental model of a neuron, on its sub-threshold dynamics. When a barrage of synchronized synaptic inputs target a cortical cell, the membrane potential is quickly depolarized and the duration of such event is prolonged by the filtering properties of the dendrites. This synchronous event thus triggers a transition of the membrane potential to a so-
called up state, which is then maintained by voltage dependent mechanisms. Following the activation of sodium dependent and calcium dependent potassium channels, the membrane potential will eventually go back to its resting level (or a more hyperpolarized one), i.e. the down state. This bistable dynamics of the membrane potential has been experimentally observed, thus our findings establishes a link between a phenomenon described at the network level (temporal correlations) and an effect observed at the single cell level (up-down states), with emphasis for the relevance of the cell morphology and voltage dependent mechanisms. Indeed, how quickly (and for how long) the cell is depolarized, following a unitary event, is crucial for the down-to-up transition to occur. If it happens too slowly and/or the depolarized state is not maintained for a sufficient amount of time, the up-state will not be generated. We found that the filtering properties of the dendrites (especially of the basal dendrites) are involved in such crucial signal transformation, as determined by a number of controls we did on the impact of the neuronal morphology.

(2) In another simulation, we studied the supra-threshold response properties (output rate and spike timing) of a target cell to changes produced solely in the higher order correlation properties of its inputs. We implemented an algorithm to generate spike trains whose higher order correlation properties could be changed, while leaving the second order ones unaffected. The output rate and spike timing of a target cell were significantly affected by these selective changes in correlation structures of the inputs. We also found significant modulation of the observed effects (increase or decrease in firing rate) depending on the selectivity of the cell for the virtual stimulation (whether we used optimal or sub-optimal virtual stimulation, respectively). Because of such differential impact of unitary events on the output rate, we proposed a link between our results and experimental phenomena related to the modulation of neuronal firing rates such as attentional effects, and gain control mechanisms.

Finally, we discussed the implication of our results in terms of cortical coding strategies. We did not propose a new coding scheme based on unitary events, per se. Instead, we used an alternative logic approach, which can be defined as “by exclusion”. In view of our results only two plausible logic alternatives are left to understand the role of unitary events in the coding problem: (a) If the assumption is made that, whatever the coding mechanisms are, they relay on spike-rate and/or spike-timing (the most commonly accepted assumption), then we showed that both these coding variables, under very general dynamical conditions (the three constraints), are
significantly affected by unitary events. If not incorporated "somehow" in the coding mechanisms themselves, unitary events are a major source of code degradation (if they would not degrade the code, despite the significant impact, it would mean that they could "somehow" be incorporated in the coding scheme). (b) If we do not assume that spike-rate and timing have any relevance for the coding problem, then unitary events might or might not be involved in the forms of computation going on in the cortex. The take home message from the above reasoning, is that following a conservative approach, we have to conclude that unitary events are involved in neuronal coding mechanisms
Riassunto

In questa tesi abbiamo studiato le proprietà statistiche degli stimoli in ingresso ad un tipico neurone corticale, con una precisione temporale del millisecondo, le proprietà neuronali di traduzione dei segnali in ingresso, e abbiamo infine analizzato le conseguenze dei risultati trovati in termini di meccanismi di codifica neuronali. Le domande cui volevamo rispondere riguardano la caratterizzazione delle proprietà di correlazione dei segnali in ingresso ad un tipico neurone corticale, e come tali proprietà possano influenzare le caratteristiche di risposta della cellula sia al di sotto che al di sopra del potenziale di soglia.

Attualmente non è possibile studiare la dinamica di pulsazione di grossi gruppi di neuroni con un approccio sperimentale diretto. Per poter misurare tale attività con un’ adeguata risoluzione spaziale (micrometro) e temporale (millisecondo), bisognerebbe utilizzare un gran numero di micro-elettrodi, inseriti nella corteccia, e registrare le risposte di diverse migliaia di neuroni contemporaneamente. Il limite attuale per questo tipo di approccio consente di registrare solo poche centinaia di neuroni contemporaneamente.


A seguito di questo risultato, abbiamo studiato l’influenza di correlazioni presenti nella dinamica di un gruppo di cellule, sulle proprietà di risposta neuronal. A tal fine abbiamo seguito due diversi approcci (rispettivamente, Capitolo 3 e 4).
(1) Servendoci di una simulazione al computer, abbiamo studiato l’effetto di eventi unitari, presenti nel network presinaptico ad un modello dettagliato di cellula neuronale, sulla dinamica al di sotto del potenziale di soglia. Quando un gruppo di input sinaptici, sincronizzati temporalmente tra loro, colpisce un neurone, il potenziale di membrana si depolarizza rapidamente e la durata dell’evento viene prolungata come conseguenza delle proprietà di filtraggio dei dendriti.Questo evento sincrono quindi provoca una transizione del potenziale di membrana verso ciò che viene definito come un stato up, mantenuto da meccanismi voltaggio-dipendenti. A seguito dell’attivazione di correnti di potassio, dipendenti sia dal sodio che dal calcio, il potenziale di membrana tornerà al suo stato di riposo (o ad uno stato iper-polarizzato), i.e. uno stato down. Questa dinamica bistabile del potenziale di membrana e’ stata osservata in diversi esperimenti, quindi le nostre osservazioni stabiliscono una correlazione tra un fenomeno tipicamente descritto a livello di network (correlazioni di impulsi neuronal), con un fenomeno osservato a livello di singola cellula (stati up e down), ponendo particolare enfasi sull’importanza della morfologia cellulare e dei meccanismi voltaggio-dipendenti. Infatti, la velocità e la durata della depolarizzazione a seguito di un evento unitario, sono cruciali affinché si realizzi la transizione tra stati down verso stati up. Se la depolarizzazione avviene troppo lentamente o non viene mantenuta sufficientemente a lungo, lo stato up non verrà generato. Infatti, abbiamo verificato che le proprietà di filtraggio dei dendriti (specialmente dei dendriti basali) giocano un ruolo importante per questo fenomeno di trasformazione del segnale, come hanno dimostrato una serie di controlli fatti per verificare l’importanza della morfologia neuronale.

(2) In un’altra simulazione abbiamo dimostrato che una cellula bersaglio risponde con estrema precisione a variazioni prodotte unicamente nella struttura delle correlazioni di ordine superiore degli input, sia in termini di frequenza di sparo in uscita, sia in termini di precisione temporale. Abbiamo generato un algoritmo in grado di produrre potenziali d’azione la cui struttura delle correlazioni di ordine superiore poteva essere controllata indipendentemente dalle proprietà di correlazione di ordine due. La frequenza in uscita ed i tempi di emissione degli impulsi subiscono cambiamenti significativi a seguito di tali variazioni, prodotte selettivamente nelle correlazioni degli input. Inoltre abbiamo scoperto che tale fenomeno viene modulato (aumento o diminuzione della frequenza) a seconda della selettività della cellula per lo stimolo virtuale utilizzato (rispettivamente, se vengono usate stimolazioni ottimali o sotto-ottimali).

Considerando l’influenza degli eventi unitari sulla frequenza in uscita dei potenziali d’azione,
abbiamo proposto un legame tra i nostri risultati e fenomeni sperimentali collegati alla modulazione delle frequenze di emissione dei potenziali d’azione, come avviene in fenomeni legati all’attenzione o meccanismi di controllo dell’amplificazione del segnale. Alla fine abbiamo discusso la rilevanza dei nostri risultati per quanto riguarda il problema della codifica. Non abbiamo proposto un nuovo modello di codifica basato sugli eventi unitari, invece abbiamo usato un approccio logico alternativo, che si potrebbe definire “per esclusione”.

Considerando i nostri risultati, ci sono solamente due alternative logiche plausibili per capire quale sia il ruolo degli eventi unitari nel problema della codifica: (a) se si assume che, indipendentemente da quali siano i precisi meccanismi di codifica, in ogni caso essi dipendano dalle frequenze dei potenziali d’azione e/o dal tempo di emissione degli impulsi (com’è comunemente ipotizzato), allora abbiamo dimostrato che ambo tali variabili di codifica, in condizioni dinamiche molto generali (i tre vincoli), sono considerevolmente perturbate dagli eventi unitari. Se non vengono in qualche modo incorporati nello stesso meccanismo di codifica, gli eventi unitari sono da considerarsi una fonte primaria di degradazione del codice (se non degradassero il codice, nonostante il loro notevole impatto, significherebbe che in qualche modo è possibile incorporarli nel meccanismo di codifica). (b) Se non si assume che le frequenze dei potenziali d’azione e/o il tempo di emissione degli impulsi abbiano alcuna rilevanza per il problema della codifica, allora gli eventi unitari potrebbero, come no, essere coinvolti in qualche forma di computazione, così come avviene nella corteccia cerebrale. Il messaggio conclusivo di questo ragionamento è che, seguendo un approccio “conservatore”, si deve concludere che gli eventi unitari sono coinvolti nei meccanismi di codifica neuronali.
I would like to express my gratitude to the several persons who supported me during these four years of Ph.D. study.

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Introduction

Neurons in the cortex integrate inputs from several thousands of other cells, e.g. (Braitenberg et al., 1998), and respond to these inputs emitting action potentials (spikes). In this thesis we study the temporal dynamics of the input spike trains to a typical cortical neuron, at a millisecond timescale, the neuronal signal-transduction properties, and how they relate to the cortical coding mechanisms.

The spatial-temporal distribution of the input to a cortical neuron is important to understand how the cell transforms the incoming signals, e.g. (Destexhe et al., 2003). To elucidate these ideas, consider the following example of a specific sensory modality, such as the visual system of a monkey. When behaving in its natural environment, the animal makes continuous saccades, exploring its visual space. Accordingly, the input to the retina constantly changes, at a timescale of a few tens of milliseconds (Moore et al., 1998). During such brief time intervals, signals (spikes) travel from the retina to the LGN, to the visual cortex1 in area V1 (Hubel, 1988). Target neurons in the primary visual area receive only a small fraction of inputs (5-10%) from the LGN (Douglas and Martin, 1990), and the majority of their connections (excitatory and inhibitory) are intracortical, from neighboring cells (Kisvarday et al., 1997; Salin and Bullier, 1995). Typically, a pyramidal cell receives 10-60,000 synaptic contacts at several dendritic locations (Braitenberg et al., 1998). Depending on which dendritic locations and when the inputs arrive (all together or “dispersed” in time? Before or after the inhibitions?), the cell might respond or not, by emitting one or more action potentials (spikes hereafter), e.g. (Taylor et al., 2000). Neuronal spikes are traditionally considered the basic “units” of information processing in theories of neural network computations, e.g. (Rieke et al., 1997), a sort of “letters” of a neuronal alphabet. Thus the study of the spatial distribution and temporal properties of the inputs to a cortical neuron is important to understand how a cell transforms its inputs, the neuronal response properties, and accordingly, the “grammatical and syntactic” rules of such neuronal language, i.e. the computational power of cortical neurons.

Despite the large amount of anatomical and physiological data at the single cell level, it is currently not known what the temporal dynamics of the inputs to a cortical cell is, at the

1 The signal goes through other pathways as well, but we want to keep the story simple.
millisecond time scale. A direct experimental approach would be optimal, though it would require simultaneous recordings of the spiking activity of a large number of neurons with a millisecond time resolution and a single-neuron spatial resolution. Unfortunately, this is not yet a feasible experimental technique. Multi electrode recordings would have the required temporal and spatial resolution, though it has not yet been possible to record from more than one or two hundred cells simultaneously (Hoffman and McNaughton, 2002). New techniques such as voltage sensitive dyes (Grinvald et al., 1988) have a good spatial/temporal resolution, but it is still not possible to go from the dye signal to the specific spiking activity of each cell in the population. As a matter of fact, there is currently no experimental technique to study the spiking activity of large groups of neurons at the temporal resolution of few milliseconds. Thus, as an alternative, we follow a theoretical approach.

I Cortical dynamics and Combinatorial Analysis.

The use of analytical tools borrowed from Physics, Statistic, and Mathematics to approach neurobiological problems has encountered major successes in the last decades. Analytical and numerical approaches have been used in a wide variety of ways: form theories of large-scale neural network studies, e.g. (Amit, 1992), to the derivation of kinetic schemes of membrane channels dynamics, e.g. (Hodgkin and Huxley, 1952). In this thesis we also use a theoretical approach based on Statistic, Combinatorial analysis and numerical simulations.

The theoretical approach used here to study the dynamical properties of the inputs to a cortical neuron at a millisecond time scale, relays on a logic procedure that can be defined as “by exclusion”. The main idea, which will be developed in detail in Section III, is that when studying the properties of a general dynamical system, it is important to exclude dynamical modalities that are not compatible with natural constraints of the system. In the specific case of the cortical dynamics, these constraints are well-established experimental results about the single cell and pairs of cell spiking activity, which limit the available dynamical states that the system can access. In essence, concerning the dynamics of the inputs to a neuron at a millisecond time scale, it is possible to exclude some population dynamics that are not compatible with given well-known physiological constraints, and, accordingly, highlight the feasible ones.
This type of logic has been so far very rewarding in the field of computational neuroscience, as demonstrated by the following example. We know from psychophysical experiments that human subjects can perform some detection tasks very quickly (few hundreds of milliseconds) (Fabre-Thorpe et al., 1998). Given that spikes travel with a finite speed from the detector (the retina) to the processing areas (LGN, V1, etc...), it follows that the initial spiking activity of the neurons activated by a given stimulus must convey a lot of information. Coding strategies that require time averages over several tens of milliseconds, such as single-cell rate coding, are bad candidates and can be excluded for being too “slow”. In this example, a fundamental temporal constraint allows us to rule out a whole family of coding mechanisms, such as single-cell rate coding, where the time averaging is done during epochs of several tens of milliseconds. It could well be that time-demanding coding mechanisms are used for different tasks, other than for fast detection, but in this very specific situation a strong statement can be made: whatever the coding strategy is, it must be either a fast temporal code or an equally fast population rate code, not a single-cell rate code (Rieke et al., 1997). Thus, as shown in this example, the logic by exclusion can give us important indications about the feasibility of different neuronal strategies.

Since we have introduced the terms rate and temporal codes, and we will continue to discuss them throughout the entire thesis, we briefly review what they refer to and how they differ from each other (Rieke et al., 1997). A rate code is a code that uses the mean number of spikes occurring in a given time window as a dynamical variable to process information. This average could refer to a single spike train for a given cell, or can be obtained by pooling together several spike trains from different neurons, thus embracing the dynamics of a large ensemble of cells. We will refer to these codes as single-cell rate codes or as population rate codes, respectively. In contrast, a temporal code emphasizes the time of spike occurrence, either in terms of absolute time in respect to a triggering event (the stimulus onset, for example, or global network oscillations), or in terms of relative timings between other spikes. The latter case represents a form of what is called a correlation code (Rieke et al., 1997). The distinction between rate and temporal codes could be more formal than substantial (Rieke et al., 1997). For example, if the mean number of spikes were counted across a population of cells in a time window of two or three milliseconds, it would be useless to distinguish between an instantaneous
population rate code and a correlation code. However, different strategies might be used in different situations and, in very natural conditions, the brain might continuously shift from one coding modality to another, as well as simultaneously use different ones.

II Fast neuronal dynamics: why does it matter for coding?

The knowledge of the global spiking activity of cortical networks, and the signal transduction properties of cortical neurons, could be of great help to unravel the coding mechanisms used by the cortex. This statement can be understood with a simple "gedanken" experiment: imagine we could sit on a neuron and observe the flow of inputs; we might question what are the temporal properties of the input dynamic at a millisecond time scale. If the input flow is fairly uniform and not very noisy (such as a quiet "river" of input spikes), it is possible that, in order to produce an output spike, the target cell might simply integrate the input spikes over time until a voltage threshold is reached. In this case, the coding variable could be the mean number of spikes in a given time window, i.e. the input rate. In contrast, if the flow is very noisy (such as a very rough, wavy river), the cell might respond more to the noise than to the mean flow. In this case, highly synchronous events in the inputs (i.e. the high "river waves") might be the major carriers of the information. Thus, depending on the temporal properties of the population dynamics, and how a neuron responds to them, it possible to narrow down relevant coding variables and, accordingly, possible coding strategies.

The computational relevance of conspicuous synchronous events (the wavy river above, also called high order correlation events or unitary events, e.g. (Grün et al., 2001)) has been widely recognized; for a review see (Salinas and Sejnowski, 2001). If high order correlation events are the relevant dynamical variables for the cells, then the underlying form of computation implemented in the cortex could be related, for example, to so-called pulsed neural networks (where the "pulses" are the unitary events) (Maass, W. and Bishop, C.M., 1999). Several theories and models followed this direction, such as the well known "synfirechain" model of Abeles (Abeles, 1991). Similarly, "binding by synchronization" (Von der Malsburg, 1981) is another example where, by using neuronal synchrony, it is possible to explain how different features in a
scene can be bound together by the visual system. Nevertheless, the key problem of establishing which of the two scenarios, as described above, is the correct representation of the fast cortical dynamics, has not yet been solved. Understanding the feasibility of unitary events as a feature of the cortical dynamics, how neurons respond to them, and to what extent, if at all, unitary events might be relevant for neuronal computation, are the main challenges this thesis wants to face.

III Structure of the thesis

To show that high order correlation events not only are an important feature of cortical dynamics, but also represent coding variables within a computational framework based on correlations, it is not a straightforward task and it requires several intermediate steps. Accordingly, we divided the thesis into four parts, corresponding to four different Chapters.

(1) In the first chapter we use a mathematical approach, based on Combinatorics and Design Theory (Beth et al., 1999) to prove that, at the level of the temporal domain of interest (few milliseconds time scale), some degree of high order correlations must emerge in the cortical dynamics. A totally uniform level of spiking activity, at the millisecond time scale, is not a physiologically realistic scenario. We start our proof by considering that this qualitative result is strongly supported by data in the hundreds of millisecond time scale, and it might be tempting to use intuitive reasoning to extend it to a shorter, millisecond, time scale. We show how this intuitive reasoning can be very misleading by introducing concepts of Design Theory, such as the Symmetric Designs. Design theory is a field of Combinatorics dealing with the problem of characterizing the statistical/combinatorial properties of large sets of elements constrained by some “rules”. We import its formalism within the framework of neuronal dynamics and use this mathematical framework to show that the dynamics of large groups of spiking neurons, constrained by high temporal variability in the single cell spiking activity and pairwise correlations in the supra-threshold domain, could in principle be totally unaffected by noise at a millisecond time scale. We discuss examples of systems with such property, i.e. the Symmetric Designs (or zero-variability systems). The use of Design Theory to infer properties about the neuronal dynamics has limitations. The most relevant for this discussion is what we call the classification problem. It is indeed not possible to classify all the symmetric designs and to match
them against physiological constraints to verify their compatibility with the cortical dynamics. Thus it could be that special symmetric designs would exist, fully compatible with known constraints about the neuronal activity. The RC-method is a statistical tool to overcome this problem. It is a statistical tool to generate very general ensembles of spike trains, including the symmetric designs and any systems with zero-noise in the millisecond time scale. By proving the incompatibility of CM systems with the subthreshold correlations constraint, we rule out the possibility that any symmetric design or zero-variability system, could be a faithful representation of the cortical dynamics. Considering the generality of our assumptions, this result proves that some degree of high order correlation events (as opposed to zero-variability systems) must characterize the spiking dynamics of a large ensemble of neurons.

(2) The second chapter relates to quantitative features of high order events (i.e. amplitude, frequency, duration, etc.). In the literature high order correlation events and unitary events are distinct concepts, e.g. (Grün et al., 2001). The distinction is based on the highly statistical significance of unitary events. If a given process is supposed to drive the activity of the neurons under study (for example, a non-stationary Poisson process), then a highly synchronous event could be labeled as a unitary event if its probability of occurrence is much above the by-chance level (significance quantified according to that specific statistical process). In this Chapter, discussing the quantitative features of the phenomena described before, we could access the statistical significance of the high order correlations existing in non-zero variability systems and, accordingly, the existence or not of unitary events in the cortical dynamics. The optimal theoretical approach would have been to find an analytical expression to related basic (experimentally determined) dynamical properties of the neurons (firing rate, CV, pairwise correlation strength) to the exact high order correlation structure of the population activity. Unfortunately this solution has a large number of mathematical problems and it is not even clear if an exact solution could in principle be found. Thus, we used again Combinatorics and standard statistical analyses to show that it is possible to compute a lower bound for the magnitude of high order correlation events. We introduce the Combinatorial Method (CM) that allows the creation of groups of spike trains whose dynamics underestimate the degree of high order correlation events in cortical networks. This is a built-in property of the Combinatorial Method, which is based on the exploitation of the combinatorial possibilities in distributing spikes between different cells, minimizing high order correlation events and, at the same time, respecting the
three above mentioned physiological constraints. Despite representing an underestimate, these systems are characterized by highly significant levels of correlated dynamics (unitary events). Thus, the significance of the results indicates that, when the three physiological constraints are satisfied, unitary events emerge in the ensemble dynamics.

(3) In Chapter 3, using a computational approach, we studied the impact of high order events on the subthreshold dynamics of a cortical neuron. We implemented a numerical algorithm to produce spike trains characterized by the presence of unitary events. We used them as input stage to a detailed compartmental model of a layer 5 pyramidal cell. When a unitary event is targeting the cell, the subthreshold membrane potential rapidly moves from its resting state to a more depolarized state, where the cell is firing. The passive filtering properties of the cell and voltage dependent mechanisms could maintain the cell in a depolarized state for few hundreds of milliseconds. The activation of sodium and calcium dependent potassium currents would eventually cause a transition back to the resting state or an even more hyperpolarized state. These transitions between different polarization states have been experimentally observed and labeled as "up-down states" of the membrane potential, e.g. (Wilson and Kawaguchi, 1996). Thus, this result about the subthreshold bistability links well known physiological data at the single-cell level (i.e. up-down states), to high order correlation properties of the network activity. Moreover, we identified four independent statistical measures of the subthreshold dynamics that correlate very precisely with the pairwise correlation strength of the network (we further develop this idea in Chapter 4). Following this result, we propose an experimental method to extract information about the network's correlation properties from intracellular recording. The novel idea is to use the cell as a probe (recording intracellular) to monitor the high order correlation properties of the network it is embedded in. The advantage of this technique is that it does not require improved methods in multi-electrode recordings, but it relies on well-established intracellular techniques. Finally, we discuss the importance of neuronal morphology in relation to the results found. We use cells with different morphologies (spiny stellate, pyramidal), and with no morphology at all (single geometrical point, Integrate-and-Fire neuron) or with different morphological parts morphed into equivalent compartments (from an electrotonic point of view). We could observe bistability only in case of intact morphology of the basal dendrites. We propose an explanation in terms of electrotonic transformation of the synaptic inputs operated by the basal dendrites: from the point of view of equivalent circuits, they can be considered as thin,
long cables attached in parallel to the soma of the cell. When targeted by a unitary event, they suddenly become iso-potential compartments, stretching in time the correlated event as a consequence of the passive cable properties of the dendrites (Rall, 1994). The overall effect is "felt" by the soma as an injection of a sustained current with a fast onset. This causes a transition to an up-state, which is then maintained by intrinsic biophysical mechanisms.

(4) In Chapter 4 we investigated the impact of high order correlation events on the supra-threshold response properties of a neuron (spike rate and timing). A key point of the chapter is the idea of isolating the impact of dynamical variations in the high order structure of the network's dynamic. All the lower-order correlation features of the population's activity are fixed and changes are produced solely in the high order correlation properties of the dynamics. We showed that neurons (using again detailed compartmental models and an Integrate-and-Fire neuron) are extremely sensitive to these selective changes. In particular, we showed that when a cell is highly responsive to a given input pattern, an increase in the frequency of unitary events, without affecting the second order correlation properties, cause an increase in the output firing rate of the neuron. Conversely, the same change causes a decrease in rate if the cell was poorly responding to the initial input pattern. This "differential sensitivity" to dynamical changes in the high order correlation structure suggests that several well known experimental phenomena (such as those related to modulations of the neuronal tuning properties and, more generally, to changes in neuronal firing rates) can find a simple explanation by considering the dynamical phenomena related to unitary events, as described above (this is discussed in more details in the last two sections of Chapter 4). Moreover, we illustrate how specific morphological features and biophysical mechanisms can work synergistically with the input correlation structures, to significantly affect the supra-threshold responses of modeled cortical cells to unitary events. The explanation we propose, similarly to the explanation provided in the previous Chapter, is that morphology and biophysical mechanisms affect the electrotonic properties of the cell, and accordingly, how the cell integrates highly synchronous events, thus producing the observed modulatory effects on the output rate. We also studied how unitary events can affect the spike timing of the target cell. In general, one or multiple spikes are produce, with a very precise temporal relationship, whenever a presynaptic high order correlation event targets the cell (see also Chapter 3). With decreasing amplitude of the correlated event, the probability of output spiking also decreases. In this sense, amplitude and timing of unitary events affect the spike
timing of the target neuron. The significant impact of high order correlation events on target cells, both in the supra- as well in the sub-threshold domain, represents the starting point, at the end of the chapter, for a discussion concerning the relevance of unitary events in terms of coding. We do not propose a specific coding scheme based on unitary events. Instead, we emphasize how, in view of our results, we are left with only two plausible logic alternatives: (1) If we assume, as it is commonly done, that spike rate and timing are the most relevant coding variables, and we consider the significant impact of unitary events on such “classical” coding variables, as discussed above, then there are two possibilities: (a) unitary events do not destroy the reliability of the coding scheme (whatever it is), being “somehow” incorporated into it. (b) Unitary events are not integrated into the coding mechanisms and will degrade its performance. (2) If we do not assume that spike rate and timing are the most relevant coding variables, then unitary events might or might not have relevance for the coding problem. In this case, alternative coding variables should be proposed. The “counterintuitive” message from the above reasoning is that, by being conservative, we should conclude that unitary events have to play a role in cortical coding mechanisms.

In the Conclusions we emphasize how the existence of unitary events in the cortical dynamics offers a possible background to unify phenomena at the network and single cell level. More in general, we discuss how the impact of unitary events on the neuronal response properties of cortical neurons implies that they are critically involved in the information processing and cortical coding mechanisms. In this respect, we speculate on the compatibility of unitary events with standard forms of neural network computations. Unitary events also offer a broader unifying framework, putting together phenomena traditionally not related to temporal correlations and fully within the domain of “rate-based” observations: for example, the results of chapter 3 and 4 suggest a “provocative” link between up-down states, attentional effects and working memory states (see more in the Conclusions). Finally, by considering our conclusions about the relevance of neuronal morphologies, we comment on the feasibility of the proposed experimental methods to validate the results of this thesis.
Chapter 1

1. Existence of high-order correlations in cortical activity

Neurons collect signals originating from a large number of other cells. The variability of this integrated population activity at the millisecond time scale is a critical constraint on the degree of signal integration and processing performed by single neurons. Optical imaging, EEG, and fMRI studies have indicated that cortical activity shows a high degree of variability at a time scale of 100s of ms. However, currently no experimental methods are available to directly assess the variability in the activity of populations of neurons at a time scale closer to that of the characteristic time constants of neurons, i.e. around 10 ms. Here we integrate pertinent experimental data in one rigorous mathematical framework to demonstrate that: (1) the high temporal variability in the spiking activity of individual neurons, (2) the 2nd order correlation properties of the spiking activity of cortical neurons, and (3) the correlations of the sub threshold dynamics, all impose high amplitude, fast variability in the population activity of cortical neurons. This implies that higher order correlations, a necessary condition for temporal coding models, must be a central feature of cortical dynamics.
1.1 Introduction

Neurons in the neocortex receive signals from thousands of other neurons (Kisvarday et al., 1997; Gabbott et al., 1987; Douglas and Martin, 1990; Salin and Bullier, 1995). The type of processing these circuits can perform depends on the cellular properties of the postsynaptic neurons and on the statistical properties of their presynaptic signals. Although knowledge about the former is quickly accumulating, our insight into the latter is more limited. In the visual system, stimulus properties change on a behavioral timescale of 100s of milliseconds. Therefore, neuronal activity shows some degree of variability on this relatively long time scale (Arieli et al., 1996). As neurons with similar response properties have a higher probability to be connected (Kisvarday et al., 1997; Douglas and Martin, 1990), this variability does not average out. However, the temporal operations performed by neurons are characterized by time constants on the order of 10s of ms. Currently no experimental techniques are available to directly measure the dynamics of large numbers of neurons at this time scale. Hence, in order to understand the fast dynamics, i.e. measured at the millisecond time scale, of neuronal populations in the cortex, we resort to a theoretical approach. In particular, we want to assess whether the temporal variability in the activity of large neuronal ensembles averages out (zero-variability systems in the following), or whether, under general dynamical conditions, some degree of fast variability must emerge. Answering this question is of great importance to understand the operating conditions of cortical neurons and their encoding capabilities: in case of zero-variability in the input dynamics to a given cortical neuron, it is exposed to a smooth sustained input current. In the opposite case of high-variability, it processes afferent signals that will vary strongly in both their total amplitude as well as their temporal properties.

A. Considerations from physiological data.

The optimal solution to directly access the fast cortical variability would be to simultaneously record the spiking activity of individual neurons in a large ensemble of few thousands of cells. Currently, simultaneous recordings of only up to a maximum number of $10^5$ neurons have been reported (Hoffman and McNaughton, 2002). Hence, the available experimental results only provide indirect hints on the fast dynamics of cortical neurons. A number of relevant observations, however, are available: (a), the membrane potential ($V_m$) variability of single
neurons at the millisecond time scale as revealed by intracellular studies (Destexhe and Paré, 2000). (b) The reliability in the spike timing (Mainen and Sejnowski, 1995). (c) The plausible pre-synaptic origin of the transition between, so called, up-down states (Wilson and Kawaguchi, 1996) and (d), the high spike timing variability, as quantified by the coefficient of variation (CV) (Stevens and Zador, 1998). All of these have been interpreted as providing indirect hints for the existence of fast variability in the dynamics of populations of cortical neurons. However, there are many alternative, equally valid, interpretations to explain these phenomena and it remains unclear whether and under what conditions, fast variability should or should not occur.

B. Considerations from modelling studies

Sophisticated statistical analyses (Martignon et al., 1995) have been used to identify patterns of activity in spike trains, interpreted as “fingerprints” of synchronous events involving a large fraction of neurons (i.e. high amplitude, fast variability) also called higher order correlation events.

In the literature, the concept of higher order correlations is used to indicate brief time intervals (few ms) during which a large fraction of cells in the population produce a spike, thus generating what is also called a population spike or unitary event (Bothé et al., 2000; Grün et al., 2001; Loebel and Tsodyks, 2002). These spiking events represent a form of fast variability in the network’s activity. Accordingly, in the present study, we will use the term “higher order events” (sometime omitting “correlation” for simplicity) to indicate the presence of fast, few ms, variability in the population dynamics, as opposed to completely uniform activity with constant, zero variability. This former case can be associated to “flat” population PSTHs (i.e. the Peri Stimulus Time Histograms of the population’s spiking activity), which indicate that, at any moment in time, a constant number of spikes is produced by the neuronal ensemble, and no higher order correlation events, or fast variability, appear.

The statistical significance of the results mentioned at the beginning of this section, however, is still hotly debated. Other theoretical studies either simply assumed the existence of higher order events (Grün et al., 2001), or focused on large-scale recurrent neural networks with simplified neuronal models (Hopfield and Herz, 1995; Amit and Brunel, 1997a; Brunel and
Hakim, 1999; Amit and Brunel, 1997b) to demonstrate that fast variability in the form of population spikes is an emergent property of the systems studied (Loebel and Tsodyks, 2002).

In summary, also in interpreting the results of these theoretical approaches, we face the problem: it is not clear under which conditions, if ever, fast variability emerges.

On a positive side, the above mentioned experimental and theoretical studies all contribute bits of information to this "puzzle", i.e. the problem of the fast variability. In the remainder of the paper we will use a number of "puzzle pieces", such as our knowledge of the pairwise correlations of neuronal activity and the CV of single cells. We will integrate these observations in a framework that will allow us to prove that under very general conditions, irrespectively of the preparation, cortical area, or species, etc., fast variability cannot cancel out. Subsequently we will consider the relevance of these results with respect to the information processing and coding strategies of cortical neurons.

C. Structure of the Chapter

After describing in detail three experimental results meant as important constraints of the neuronal dynamics, (section 0-D), section I faces the question, using formal mathematical arguments, of whether it is possible to have zero fast variability in the activity of large ensembles of cells, given our experimental and theoretical knowledge of the cortical dynamics. We describe systems (ensembles of spiking neurons) without fast variability (I A-B) and check their compatibility with physiological constraints (I C). We will make use of Design Theory, a branch of Combinatorics, to provide examples of dynamical systems that are characterized by a total absence of fast variability and that are still fairly compatible with physiological constraints. This suggests that a more careful analysis is required to support the commonly held notion of non-zero variability in the short time scale. At the end of section I, we describe the problem of classifying such systems in a formal and exhaustive way, which leads us to abandon the formalism of Design Theory in favor of a more classical statistical one. In section II, in order to solve this "classification problem", we introduce a statistical approach (RC-method, II A-B) to describe any systems with zero fast variability (including those introduced in the context of Design Theory in section I) and verify again their compatibility with physiological constraints, II C-D. Finally, in
section III we prove the incompatibility of such systems with the cortical dynamics. These steps allow us to formally prove that higher order correlations must exist in cortical dynamics. The implications of this observation will be further elaborated in the discussion.

D. Physiological constraints on neuronal processing.

In order to assess whether a model accurately describes the cortical dynamics, it needs to satisfy a number of physiological constraints. The three constraints considered here are:

(C1) High temporal variability observed in the spiking activity is quantified by the coefficient of variation (CV) (Teich et al., 1997), which is defined as the ratio between the standard deviation and the mean of the Inter-Spike-Intervals (ISI). The CV of cortical neurons is measured to be 1 or more, a variability that exceeds that of a pure Poisson process (Rudolph and Destexhe, 2001).

(C2) Second, the spiking activity of pairs of neurons in the primary visual cortex shows a correlation that is proportional to the similarity of their feature preference (König et al., 1995a; Singer, 1993). These experimentally observed correlations are "weak" in the sense that only very few spikes between pairs of spike trains are correlated. Typical correlation strength, measured as the peak amplitude of the cross-correlogram over the offset (König, 1994), is about 0.1 (König et al., 1995a; Singer, 1993; Salinas and Sejnowski, 2001; Singer and Gray, 1995) implying that only 1 out of 10 spikes is in some specific temporal relationship (König et al., 1995b). This weak pairwise correlation has been observed in several cortical areas, in different species, and in anaesthetized as well as in awake behaving animals (Singer, 1993).

(C3) Paired intracellular recordings in primary visual cortex have detected correlations in the subthreshold membrane potentials of neighboring neurons (Lampl et al., 1999; Stern et al., 1998). It has been shown (Lampl et al., 1999) that the normalized peaks of the cross-correlograms range around 0.4, which indicates that 40% of the time, the sub threshold membrane potential of

1 To help the reader follow the logical structure of the Chapter we will begin and end relevant sections, which are not pure formalisms or definitions, with an "Introduction" and "summary" paragraph respectively, each of them terminated by a "•" symbol. The reader who is not interested in the mathematical proofs can then easily follow the backbone of the logical structure, reading only those paragraphs.
neighboring cells in visual areas is correlated. This correlation is amplified during visual stimulation with normalized peaks as big as 0.8 (Lampl et al., 1999).

Here we address the question how the above properties of cortical neurons, i.e. high CV, sub- and supra-threshold pairwise correlations, constrain the overall dynamics of cortical networks in the short time scale. We prove that in a neuronal ensemble, during high-input regimes, some degree of variability must exist.

1.2 Zero-variability systems: compatibility with C1 and C2.

In order to characterize the fast variability of cortical neurons, the second and higher order statistical properties (i.e. mean firing rate, pairwise correlation strength, and unitary events) of the input activity to any given target cell, comprising 5000 to 20,000 input spike trains (Salin and Bullier, 1995), need to be defined (König et al., 1995a; Douglas and Martin, 1990; Salinas and Sejnowski, 2001). A qualitative observation gives an intuitive idea of a possible solution.

Considering that the number of pairwise coincidences rises quadratically with the number of afferents, and that the number of spikes available to generate such coincidences rises only linearly with the number of afferents, it follows that spikes have to be "used" multiple times to generate coincidences, i.e. higher order correlations must appear. However, this intuition can be misleading and it raises the question whether the emergence of higher order events is a necessary consequence of the experimental constraints.

Introduction: Here, we use systems (Symmetric Designs) that are well known in the field of Combinatorics and Design Theory (Beth et al., 1999; Assmus and Key, 1992), but not yet introduced in the study of cortical systems. For our very basic use of Design Theory, it is just necessary to know that this field of mathematics is extremely helpful in identifying features and emergent properties of large-scale complex systems constrained by "some" limitations. To provide an intuitive example of what we mean with complex system, one can imagine a raster plot of the spiking activity of a large ensemble of cells. Design Theory helps to understand the structure of such plots, and equivalently, the properties of the corresponding population PSTH.

In the fields of Combinatorics and Design Theory (Beth et al., 1999) systems have been identified that have zero variability in their PSTH ("flat" population PSTH) and non-zero pairwise correlations. For some of these systems the constraint of high CV is also satisfied. We
now verify in detail the compatibility of these systems with the three physiological constraints introduced above individually. In the last paragraph of section B we will provide a clear example to give an intuitive idea of how symmetric designs can be generated and in which way they could relate to cortical dynamics.

A. Definitions and formalism: redefining the problem

It is useful to think of a spike train as a binary string where the "ones" represent the occurrence of a spike and the "zeros" a non-occurrence. The length of the string is defined by the duration of the single "bins", $\Delta_{\text{bin}}$, which are used to discretize the spike train, and the number of bins, $N_{\text{bin}}$. This is essentially the time resolution of the system: $\Delta_{\text{bin}} \cdot N_{\text{bin}} = T$, with $T$ being the total duration of the spike train. The string of time bins can be thought of as a group $S = \{s_1, ..., s_w\}$ of elements. Considering that the spikes can occur in any time bin, all elements between $\min(S)$ and $\max(S)$ must be included, and it is always possible to shift the elements such that $\min(S) = \lambda_{\text{start}}$. In general, $S$ can be thought of as a permutation of the elements of the set $\{\min(S), ..., \max(S)\}$. Therefore, the problem can be viewed in a finite field $Z_n$, for some integer $n$. Given these definitions, we assume that $S = \{0, 1, 2, ..., N_{\text{bin}} - 1\}$, and that any spike train can be represented by a subset $C = \{c_1, ..., c_k\}$ of $S$. In order to faithfully represent the spike train we want every element in $C$ to carry information about the spike timing. For example $c_1 = \lambda$ means that a spike occurs at a time $\Delta_{\text{bin}} \cdot \lambda$. If the firing rate is constant then the size of every subset is of a fixed value $k$. Suppose we have $C_1, ..., C_m$ as distinct non-empty subsets (spike trains), then the weak pairwise correlation constraint (C2) translates to $|C_1 \cap C_2| = q$, for any pair of subsets, with $q$ being a fixed parameter defining the number of overlaps (the strength of the correlation).

B. Symmetric Designs

For the systems with a flat population PSTH described in Design Theory, the number of subsets $m = N_{\text{bin}}$, and these objects are called Symmetric($N_{\text{bin}}, k, q$) - Designs(Beth et al., 1999; Assmus and Key, 1992).
One well studied example of Symmetric Design is the so called Fano plane, Fig. 1(a): In this case $N_{bm} = 7$. The Fano plane is a $p=2$ symmetric design, which means that $N_{bm} = p^2 + p + 1$, $k = p + 1$ and $\lambda = 1$, so blocks of different sizes can be created using higher $p$-values. Other examples of large-scale Symmetric Designs are the so called Hadamard Designs (symmetric $(4t-1, 2t-1, t-1)$-designs); projective planes (symmetric $(p^2+p+1, p+1, 1)$-Designs), etc.

Figure 1

(a) Representation of the Fano-plane, projective plane of order 2, a symmetric $(7,3,1)$-design. This "squared grid" can be associated to a raster plot of spike trains in the following way: every row represents the spiking activity of a single cell (seven in this example), where the occurrence of a spike is a filled circle and the non-occurrence is simply an empty box. Note that the number of elements (filled circles, or "spikes" in the raster plot representation) along the columns is constant and equal to that along the rows (or spike trains), as indicated by the side histograms. (b) Example of a "graph" and its associated incidence matrix. (c) Schematic of the mathematical space where the described objects can exist. The light gray oval, symbolizes the border of the group of zero-variability systems (ZVB), while the black oval is the border of the group of average RC-systems, ($<\text{RC}>$). This latter group includes classified (C) and unclassified (U) Symmetric Designs (the circles with the corresponding letters), which satisfy the constraints of high $CV$, indicated with the letter (a), and of pairwise correlations for the spiking activity, (b), but not the constraint for the sub-threshold correlations, crossed (c). The space between the ovals, indicated simply with RC, represents in general the systems (open circles) produced by the RC-method, which deviates from the average behavior, i.e. small $N$ and duration time. For these cases, $CV$ and correlation strengths cannot be fixed. (d) Histogram of the peak values of the subthreshold cross-correlated activity, adapted from Lampl et al. 1999.
1. **Symmetric Designs interpreted as raster plots.**

We can interpret the Fano plane (and any Symmetric Design) as a raster plot, Fig. 1(a). If we assume that each of the seven columns represents an interval of 5 ms, i.e. the time resolution, the Fano plane represents the raster plot of seven neurons for a total trial duration of 35 ms. The filled circles represent the occurrence of a spike for the corresponding cell at a given time. For example, cell 4 emits three spikes, the first spike in a time between 0 and 5 ms, the second spike between 15 and 20 ms and the third between 30 and 35 ms. All the cells have the same mean firing rate (every row has 3 spikes). Moreover, the neurons show a fixed pairwise correlation since, taken any of the possible pairs of cells, only one of the three spikes for each cell is located in the same column as for another cell. For example, both cell 2 and 6 emit a spike in a time between 10 and 15 ms and that is the only time overlap. The histogram at the bottom represents the population PSTH, which is characterized by zero variability. A large number of Symmetric Design systems have been reported in the literature (Beth et al., 1999). Hence, to create a system that implement a cortical raster plot with an arbitrary number of cells and of any duration, characterized by variability at the 100s ms time scale and no variability at the 10s ms time scale, turns out to be very easy. Several Symmetric Designs (as the Fano plane), with duration of few 10s of ms, each with the same rate and correlation properties, can be vertically (temporally) aligned to obtain the desired number of rows (neurons in the population). This would form the first “block of columns”, i.e. the raster of the population for the first few 10s of milliseconds. To provide the second and following blocks of columns (i.e. the complete temporal evolution of the system), Symmetric Designs with different mean rate can be used. This way the global population PSTH would show variability only in 100 of milliseconds time scale and not on a shorter time scale. Having this generating mechanism in mind, we will neglect in the following the global dynamics and focus on the “building blocks”, i.e. the Symmetric Designs.

**Summary:** Symmetric Designs can be used as “building blocks” to produce raster plots (and from those PSTHs) characterized by a global variability at the 100s ms time scale and no variability at the 10s of ms time scale. Such systems exhibit weak pairwise correlations, C2, as experimentally observed in the dynamics of cortical neurons.
C. The coefficient of variation constraint (C1)

Introduction: To claim that Symmetric Designs can successfully describe the cortical dynamics, we need to verify their compatibility with the other constraints, C1 and C3. In this section we will focus on C1, i.e. high temporal variability in the single cell spiking activity.

In Design Theory, systems with high CV (Coefficient of Variation of inter-spike-intervals) can be found when studying the so called cyclic difference sets (Beth et al., 1999), an example using arithmetic mod(13) in the field $\mathbb{Z}_{13}$ is given in the Appendix 1, supplementary Fig. 1(a).

In this example, there are two remarkable features: the exponential that describes the distribution of the inter-spike-intervals is necessarily incomplete and "pathological" cross-correlation structures, always strongly asymmetrical (i.e. non-zero abscissa for the main peak) are produced, Appendix 1, supplementary Fig. 1(b).

None of the above zero-variability systems can describe the real cortical dynamics. They do not satisfy either the CV or cross-correlation constraint. Unfortunately, satisfactory examples cannot be found either in the context of Graph Theory (Berge, 1962), which focuses on the properties of the incidence matrix, Fig. 1(b), or advocating the so-called balanced incomplete block designs (BIBD, see T. Beth et al. 1999 for a formal definition).

Summary: When detailing the compatibility of Symmetric Designs with C1 and C2, problems arose in finding satisfactory examples. Nevertheless, no proof is available that at least one "good" system does not exist. We cannot proceed by enumerating examples, because "classifying these objects is clearly impossible with present methods" (Jungnickel, 2002), i.e., we cannot make a list of all Symmetric Designs and exclude them one by one. Design theory has been useful to disprove the intuition that C1-C2 are sufficient to enforce higher order correlations. Nevertheless, to continue we have to utilize an additional approach, and return to symmetric designs further down.

1.3 The classification problem and the RC-method.

Introduction: To circumvent the above mentioned classification problem and give a formal proof that zero-variability systems are not compatible with cortical dynamics at any time scale, we introduce a statistical method, the RC-method (an intuitive idea of how the RC-method works
is given in the first paragraph of session II A). This allows us to define statistical quantities, which can be directly compared with physiological and biophysical results, C1, C2 and C3. This discussion will take all section II. Only in section III we will solve the above mentioned classification problem. At the end of section III we will summarize the results and provide conclusions in relation to this statistical approach.

A. An introduction to the RC-method

To give a clear idea about what the RC-method is, we could interpret again the incidence matrix associated to the Fano plane, Fig. 1(a), as a raster plot. At every time step a fixed number of cells, \( k \), are specifically selected by what we call a controller, to make them spike, and the Symmetric Design structure is produced. More specifically, referring to Fig. 1(a), a generator of integers (i.e. the controller) would produce the sequences of triplets: \((4, 5, 7), (1, 3, 7)\) and so on. These numeric sequences would simply mean that a filled circle (spike) should be assigned in the first column at row 4, 5 and 7, in the second column at row 1, 3 and 7 and so on, until the structure of the Fano plane is created. The raster plot of the Fano plane can then be considered as a possible subset of integers generated by a random-uniform generator of numerical sequences (RC-method). Indeed, going back to the previous example, the specific sequence of integers that would create the Symmetric Design, \((4, 5, 7), (1, 3, 7)\) and so on, is a special choice between those that a random generator of triplets of integers can produce. Given the proper value for \( k \), this method ensures that any pair of rows has, on average, the same number of intersections (fixed correlation strength) and all the rows contain the same number of spikes (fixed firing rate). From these considerations we can formulate the first important theorem.

**Theorem 1:** Any zero-variability system, with any pairwise correlation property, can be generated by the RC-method.

**Proof:** Given a zero-variability system, however generated, it can be mapped into a binary matrix of zeros and ones as in Fig. 1(b), which shows its incidence matrix. The total number of elements along the columns must be constant by definition of zero variability. The row-indices of the selected cells at every time step are \( \xi \) integers \((4, 5, 7; 1, 3, 7; \text{etc. in the previous example})\). The whole system can then be described by a sequence of integers of length \( \frac{T}{\Delta t_{\text{bin}}} \times \xi \), i.e.
Chapter 1

proportional to the total duration, $T$, divided by the time resolution, $\Delta t_{\text{bin}}$. There is always a non-zero probability that a random generator can produce such a sequence. 

The concepts proposed here are schematized in Fig. 1(c).

B. Formalism for the RC-method

In section A we said that the RC-method can generate systems with fixed second order statistics i.e. firing rate and pairwise correlations. We want now to better characterize this statement and to analyze the limitations of the method as well.

For fixed firing rate $f$ and pairwise correlations strength $c$, a given cell $a$ correlates with cell $b$ on average, every $T_2 = \frac{1}{f \times c}$ seconds; i.e. $c$ determines the mean time between two correlated spikes. However, the mean time before two spikes correlate again is also determined by the probability, $P_r$, that the controller will reselect the cells $a$ and $b$. From combinatorial analysis and by indicating the number of cells with $\gamma = 2$, we have $P_r = \frac{(N-\gamma)^{n-\gamma}}{N^n}$, where $n$ is the number of spikes assigned at every step by the RC and $N$ is the total number of spike trains. For $\gamma = 1,2$, the previous expression can be approximated by $P_r = \left(\frac{n}{N}\right)^{\gamma}$, this way

$$T_1 = \left(\frac{N}{n}\right)^2 \times \Delta t_{\text{bin}}, \text{ with } T_1 \text{ the average time of co-selection of a given pair of cells.}$$

The method can produce systems according to the correlation and firing rate constraints, $c$ and $f$, if the following condition is satisfied: the average frequency of occurrence of the intersections as determined by $c$, and the frequency of the random controller in selecting a given couple of cells must be the same. This results in the following condition, $T_2 = T_1$, which is true if $n = N \times \sqrt{f c \Delta t_{\text{bin}}}$. This is what we call consistency condition.

**Theorem 2:** The RC-method satisfies the consistency condition if $f \Delta t_{\text{bin}} \geq c$.
Proof: If the process selects a given cell $a$ with a frequency $\frac{1}{T_1}$ for the correlation constraints with cell $b$, this is also true in respect to the correlation constraints with all the other cells. Indeed, the frequency used by the controller to select a given cell can be computed from its probability of selection. For $\gamma = 1$, $P_i = \left(\frac{n}{N}\right)^y$, so the controller is selecting any given neuron with a frequency $f_{pr} = \frac{n}{N \times \Delta_{bin}}$. Using the expression for $n$ as above, we get the following expression, $f_{pr} = \sqrt{\frac{f_{cs}}{\Delta_{bin}}}$. Since the selection of a cell corresponds to a spike insertion as well, it is necessary that $f_{pr} \leq f$ which means that $f\Delta_{bin} \geq c_s$.

C. Consistency with cortical dynamics?

For typical values of $c_s = 0.1$ and $\Delta_{bin} = 1ms$ (Köng et al., 1995a), $\frac{c_s}{\Delta_{bin}} = 100$, so the consistency condition is achieved only for firing rates greater than 100 Hz, which is clearly not the mean rate of a cortical neuron (Connors and Gutnick, 1990; McCormick et al., 1985). Yet, increasing the value of $\Delta_{bin}$ or decreasing the value of $c_s$, can lead to values of $f$ that are within those reported, assuring the consistency. Thus, the two constraints applied so far are not sufficient to exclude a zero variability population PSTH.

D. Confronting the RC-method with the sub-threshold correlation constraint (C3).

We use now the third constraint, regarding the subthreshold correlations, to further narrow down the range of validity of zero-variability systems.

Theorem 3: The maximum and minimum fraction of time, $T_r$ and $T_s$, respectively, during which two cells, whose spiking activities are produced by the RC-method, can be correlated, is given by
\[ T_f = 1 + \Delta_{dec} \times \left[ f_C - 2 \sqrt{\frac{f_C}{\Delta t_{bin}}} \right] \quad \text{and} \quad T_u = \Delta_{corr} \times \left[ f_C + 2 \sqrt{\frac{f_C}{\Delta t_{bin}}} \right] - 2\Delta_{dec} \times \sqrt{\frac{f_C}{\Delta t_{bin}}} ^2 \]

**Proof:** We first demonstrate the equality for \( T_f \). As shown in Fig. 2(c) (left panel), in between two correlated spiking episodes of cell 'a' and 'b' (dark gray spikes on the sides), the average distribution in time of the uncorrelated spikes (light gray spikes) is such that between two consecutive spikes of cell 'b' there will be a spike of cell 'a'. This is because the RC-method by definition minimizes the temporal overlaps between the spiking activities of the two cells. We call \( \Delta_{dec} \) the time interval centered around the uncorrelated spikes of cell A and B, during which the membrane potential of the two cells cannot be correlated. This is simply due to the up-down swing of the action potential; if a cell is spiking and the other is not, the stereotyped shape of the action potential implies that the correlation coefficient between the two membrane potentials is necessarily very small, Fig. 2(a). From the consistency condition of Theorem 2, we know that the average inter-spike-interval is \( T_{pr} = \frac{\Delta t_{bin}}{f_C} \) and the average distance in time between two correlated spikes is \( T_1 = T_2 = \frac{1}{f_C} \).
Figure 2

(a) When performing paired intracellular recordings from neighboring cells, a possible dynamical scenario could be characterized by common subthreshold fluctuations where in between correlated episodes, only one of the two cells spikes due to some fast noise, while the other does not. Because of the up-down swing of the action potential the correlation coefficient between the two traces computed in a time interval equal to the absolute refractoriness (Δt_{ref}), is low, but excluding such brief event, the activity of the two cells could be on average correlated (Δt_{corr}). (b) This curve schematically reproduces the experimentally derived one as shown in Figure 1(d). The parameters T_f and T_u can be related to the upper and lower tails of the distribution respectively. (c) The left panel illustrates the method used to derive T_f (see text for the detailed derivation). Δt_{ref} refers to the duration of the up-down swing of the action potential (absolute refractoriness), T_{pr} is the inter-spike-interval as derived by the RC-method, T_i is the mean time of occurrence of correlated spikes. The shaded areas are the time intervals used to compute the “free-time” parameter. The right panel instead relates to the derivation of T_u. The main difference is that the shaded areas represent the intervals during which the two cells are for sure correlated (Δt_{corr} - Δt_{ref}). (d) The three panels show T_f and T_u as a function of Δt_{corr} for three different values of the mean firing rate: 30, 60, and 80 Hz respectively. The five different horizontal and oblique lines refer to T_f and T_u while
Δt_{dec} changes from 1 to 5 ms respectively (1 for the top lines and 5 for the bottom lines). The two vertically aligned filled circles in the first panel indicate the values of $T_f$ and $T_u$ (from bottom to top respectively), given a distribution whose mean is around 0.4, as in Figure 1(d).

Given these definitions we compute the fraction of the total time available for possible subthreshold correlations between cell pairs, called “free-time”, $T_f$. This parameter represents the upper tail of the distribution of the subthreshold correlation coefficient (Fig. 2(b)). This is because if during the available “free-time”, the two cells are indeed always correlated, the maximum possible correlation coefficient would be achieved. This “free-time” is schematically shown by the shaded areas in Fig. 2(c) (left panel). Its fractional value, obtained normalizing for a given inter-spike-interval, is

$$T_f = \frac{T_{pr} - 2\Delta t_{dec}}{T_{pr}} + \frac{\Delta t_{dec}}{T_1}$$

where the last term on the right hand side comes from the consideration that correlated spikes add to the “free-time”. Using the expressions for $T_{pr}$ and $T_1$ as defined above, we get

$$T_f = 1 + \Delta t_{dec} \times \left[ \frac{f_{cr} - 2}{\Delta f_{IIR}} \right].$$

We proceed in a very similar way to compute the fraction of time during which two cells are necessarily correlated, $T_u$. This would represent the lower tail of the distribution of subthreshold correlation coefficients as in Fig. 2(b). First, we need to recall an experimental observation: when computing the cross-correlograms of the membrane potentials, Lampl et al. found that the widths of the peaks of these cross-correlograms were much broader than those computed for the spiking activity (Singer, 1993). The mean value reported was around 40 ms for $V_m$ vs. <10 ms for the spiking activity (Singer, 1993; Lampl et al., 1999). This number indicates that when two cells are in a correlated state, they will on the average stay correlated for a duration comparable to the width of the cross-correlograms. We use this observation to introduce a correlation interval, $\Delta t_{corr}$ ($\Delta t_{corr} > \Delta t_{dec}$), which is also centered around each spike. During $\Delta t_{corr}$ the two cells are necessarily correlated (excluding the brief interval during the occurrence of the spike, $\Delta t_{dec}$; see Fig. 2(a)). $\Delta t_{corr}$ can be justified in the following way: $\Delta t_{dec}$ has been defined before based on the stereotyped shape of action potentials. Hence, outside this time interval, we have no hypothesis about the correlation properties of the membrane potentials. Suppose instead that we have been able to measure the mean value of $\Delta t_{dec}$, then right outside this interval the two cells must on average, by definition, be correlated. An example of this scenario for the subthreshold
dynamics is schematically shown in Fig. 2(a): both cells might depolarize towards threshold simultaneously, but only one emits a spike. During such an episode, the $V_m$ of the two cells is strongly correlated, $\Delta t_{corr}$, except during the swing of the action potential, $\Delta t_{dec}$. The shaded areas in Fig. 2(c) (right panel) represent the time during which the two membrane potentials must be correlated for a given inter-spike-interval. The fractional value is then

$$T_u = \frac{2\Delta t_{corr} - 2\Delta t_{dec}}{T_{pr}} + \frac{\Delta t_{corr}}{T_1},$$

where the last term on the right side of the equation comes from the consideration that correlated spikes add to the time during which the two cells must be correlated. Using the expressions for $T_{pr}$ and $T_1$ given above we get

$$T_u = \Delta t_{corr} \times \left[ f c_s + 2 \times \sqrt{\frac{fc_s}{\Delta t_{bin}}} \right] - 2\Delta t_{dec} \times \sqrt{\frac{fc_s}{\Delta t_{bin}}}.$$

We now want to check if there is a set of parameters ($\Delta t_{corr}, \Delta t_{dec}, f, c_s$), such that $T_f$ and $T_u$, i.e. the higher and lower tails of the distribution of correlation strengths, are compatible with the experimental data (Fig. 2 (d)). Every panel relates to a different average firing rate, $f$, and it shows $T_f$ and $T_u$ as a function of $\Delta t_{corr}$ for different values of $\Delta t_{dec}$ with $c_s$ set to 0.1. The thick horizontal and vertical lines at 0.4% and 10 ms indicate the mean correlation value as experimentally observed and the typical average width for cross-correlograms of pairs of spike trains, respectively. The dotted horizontal lines correspond to different $T_u$ values while $\Delta t_{dec}$ is increasing from 1 to 5 ms (going from the top to the bottom respectively). In the same way, the oblique lines show the behavior of $T_u$. The results demonstrate that there is NOT a set of values such that $T_f$ and $T_u$ would match the distribution found by Lampl et al. (Lampl et al., 1999). A very narrow distribution with a mean around 40% (as reported by Lampl et al.) can be obtained for $f \leq 30$ Hz, $\Delta t_{corr} < 10$ ms, and $\Delta t_{dec} = 5$ ms, as qualitatively indicated by the filled circles in the left part of panel ‘c’, corresponding to the filled circles shown in panel ‘b’. These values for $f$, $\Delta t_{dec}$, and $\Delta t_{corr}$ are not compatible with the observed data and the dynamical conditions studied here, i.e. high input regimes. The conclusion is that the temporal distribution of the spikes produced by the RC-method is not consistent with the subthreshold correlation properties observed in the experiments.

The incompatibility of the RC-method with the physiological data results from its inability to capture the pertinent correlation statistics. This suggests that in order to satisfy the
constraints C1-C3 some degree of temporal alignments must occur. We evaluated this contention using a numerical simulation.

**Numerical Simulation:** We show numerically that for systems that are statistically very close to those generated by the RC-method, i.e. zero-variability systems, the $T_f$ parameter is too low in respect to the experimentally reported values. Moreover, we show that only allowing variability in the population PSTH, it is possible to obtain values compatible with the experimental ones. We considered as an approximation of an RC-system a group of uncorrelated Poisson spike trains. This is a simplification since Gaussian noise characterizes its dynamics, i.e. non-flat population PSTH. We then designed an algorithm to produce weak pairwise correlated spike trains, allowing some degree of temporal alignments and high CV. Results for this simulation using a mean rate of 85 Hz and $\Delta t_{dec} = 4$ ms, are shown in Fig. 3. The lower plane (uncorrelated Poisson trains) shows a 35% value for the free-time parameter, while 55% is obtained for the correlated system, compatible with reported experimental values, Fig. 1(d). The two systems have the same CV and mean firing rate, but they differ in the correlation statistics. The important observation is that systems with some degree of temporal alignments are characterized by a free-time parameter that is compatible with C3. This does not hold true for the uncorrelated Poisson case. The high variability close to the origin of the plot and the asymptotic behavior are important features, which will be discussed later on. Increasing the firing rate to 90 Hz leads to a decrease of $T_f$ for the uncorrelated system to 30% and when widening $\Delta t_{dec}$ to 5 ms, an additional reduction to 17% is observed. The algorithm allowed us to vary the degree of temporal alignments and accordingly the correlation strength: For $\alpha = 0.2$ and unchanged rate and high CV, $T_f$ reached 60%.
Figure 3. Simulation results. The free-time parameter, \( T_f \), is plotted against the total number of cells and the duration of the time window used to compute the mean value of the parameter for each couple of spike trains. Such mean has been computed averaging \( T_f \) values obtained from all possible combinations of two spike trains for a given number of cells in the sample. The upper trace refers to an ensemble of spike trains having weak pairwise correlations (\( C_s = 0.1 \)). The lower plane instead refers to uncorrelated Poisson spike trains. In both cases the firing rate was fixed to 85 Hz. In the correlated case, characterized by temporal alignments in the spiking activity, the free-time parameter shows a higher value than for the uncorrelated case, 55% and 35% respectively. Higher variability at the origin for both the planes is contrasted by a stable convergent behaviour in ensembles having more than 2-3 cells and whose duration last longer than 100 ms.

Note: Looking at the results there are two important observations: First, the expression for \( T_f \), as soon as \( N \) is greater than 3, does not critically depend on \( N \). Second, the variability associated to the uncorrelated Poisson system does not produce a free-time parameter compatible with \( C_3 \). This not only suggests that non-flat population PSTHs are necessary to match physiological conditions, but also that the required variability should exceed that of an uncorrelated Poisson system.

Summary: The RC-method is a very general statistical approach to produce any system with zero fast variability, including the Symmetric Designs. When confronted with the physiological constraints \( C_1 \), \( C_2 \) and \( C_3 \), the systems generated by the RC-method do not fulfill the subthreshold constraint, \( C_3 \). Some degree of temporal alignments, or synchronized activity, is necessary. A numerical simulation supports these results.
1.4 Excluding the Symmetric Designs.

Introduction: The average statistical behavior of systems generated by the RC-method, including the Symmetric Designs, is not compatible with the three constraints described at the beginning. The third one, concerning the subthreshold correlations, plays a major role. We went around the “classification problem” and found a more general solution to create zero-variability systems and to verify their compatibility with the cortical dynamics. These results can be naturally extended to the Symmetric Designs.

The following lemma will answer the question whether or not zero-variability systems can describe cortical dynamics constrained by C1, C2 and C3, thus solving the classification problem presented in section II C. It comes simply as a corollary of Theorem 3.

Lemma 1: Symmetric Designs cannot describe cortical dynamics as defined by: (a) high CV at the single cell level; (b) pairwise correlations for the spiking activity; (c) pairwise correlations in the sub-threshold domain.

The proof is given in the Appendix 1. Note that proving Lemma 1 is a central point to support the logic consistency of the paper: Symmetric Designs have been here very useful to exemplify why C1 and C2 cannot help in constraining the higher order correlation properties of the dynamics, which has been a controversial issue since the introduction of the synfire chain model by Abeles (Roskies et al., 1999; Abeles, 1991). However, at the end of Section I, we could not solve the classification problem. If not resolved, there would have been the possibility that a “special” Symmetric Design, obeying C1-C3, could represent the cortical dynamics characterized by zero variability in the few ms time scale. Lemma 1 proves this is not possible.

From Theorem 3 and Lemma 1 it follows,

Theorem 4: Dynamical systems that satisfy the constraints of sub- and supra-threshold correlations and high CV must display higher order events in the population dynamics.

Proof: This is guaranteed by the validity of Theorem 3, Lemma 1 and from the observation that systems that are the complement of zero-variability ones (in mathematical terms) must have, by definition, some degree of variability, i.e. some degree of higher order events. Moreover, the generality is guaranteed by the fact that the RC-method can embrace all the systems with zero-variability (Theorem 1). When the first two constraints are imposed, i.e. high CV and pairwise correlations for the spiking activity, any zero-variability system must behave according to the
average behavior of the RC-systems (see proof in lemma 1) and consequently be disregarded, since it cannot satisfy the third constraint.

Summary: To solve the classification problem we used the RC-method. This allowed us to generate a larger group of systems characterized by a flat population PSTH, which included, as a subgroup, the Symmetric Designs. When checking for the compatibility between such systems and the constraints C1, C2, and C3 (i.e. supra-, sub-threshold pairwise correlations and high CV) we found a negative answer, mainly for what concern the sub-threshold correlations. Flat population PSTHs, and Symmetric Designs as well, cannot be compatible with a cortical dynamics constrained by C1, C2 and C3. Under these conditions, some degree of variability must appear even in the 10s of ms time scale.

1.5 Discussion

Here, we showed that the available experimental data on the high temporal variability existing in the spiking activity of individual cortical neurons, together with their pairwise correlation properties, enforce non-zero variability in the activity of populations of cortical neurons. Thus, the variability in the activity of a large number of neurons converging onto a common target does not average out. Although this was known for the slow cortical dynamics, at a timescale of 100s of ms, our results show that this is true also for the fast variability, in the few 10s of ms timescale. Although earlier theoretical work had suggested that this could be the case, a direct experimental or formal proof was missing. Hence, the contribution of our analysis is that by putting together fragmentary theoretical and experimental knowledge, it formally demonstrates under which general conditions fast variability must be observed. Whenever the three constraints C1, C2, and C3 hold, fast variability must be observed irrespective of the preparation, type of cells, species etc. To develop our proof we have made use of Design Theory. With this approach, we could identify zero-variability systems that we subsequently matched against physiological constraints. We expect that this mathematical framework, new to computational neuroscience, might turn out to be a useful tool for further analyses of the complex dynamics of neuronal systems.

For our formal analysis, we relied on a number of experimental results, and we have to assess whether these apply under the relevant conditions. The numerical estimates we have used, refer to values of the correlation strength, mean firing rate, and CV obtained in several species.
and cortical areas. However, many experiments are performed under anesthesia, and data on the neuronal dynamics in awake animals is practically not available. The situation with respect to the third constraint, subthreshold correlations, is even more problematic. Due to the immense technical difficulties of these recordings, only few reports are available (Lampl et al., 1999; Stern et al., 1998). On the positive side, we have no reason to doubt that the results obtained in other species and cortical areas will be qualitatively different. Furthermore, the paradigms cited are those that form the backbone of much of experimental neurophysiology of the mammalian cortex. In this sense, the constraints we have considered reflect the state of the art in current neuroscience and we believe that our results are of general relevance.

Experimental data and theoretical studies can be put together to provide a comprehensive view and formally solve the problem of fast variability. Understanding this issue is of key relevance mainly for clarifying the consistency and feasibility of different neuronal coding mechanisms, which in one way or another do make assumptions on the fast variability. Indeed when considering widely used rate-based models, the key dynamical variable is the rate, i.e. the total count of inputs in a given time interval. Fast variability in the population activity, however, is a source of code degradation (Mazurek and Shadlen, 2002). Population spikes induce high-amplitude "noise" in the inputs, thus degrading the reliability of its spike count. Moreover, they can elicit spikes by a target cell degrading its information transduction. The optimal working regime for such coding mechanisms would be a total absence of fast variability. In contrast, correlation-based models rely on higher order correlation events, as a key dynamical feature used in information processing (Von der Malsburg, 1981) (Abeles, 1991). Neurons, acting in a coincidence detection mode, are supposed to be strongly responsive to such unitary events. These correlation phenomena are a central feature for temporal coding schemes and their computational relevance has been extensively explored in theoretical studies (Roskies et al., 1999). By providing general statements on when fast variability is necessarily observed in cortical dynamics, our study elucidates under which dynamical conditions the different coding mechanisms can work consistently and optimally.

At a cellular level, the results presented here contribute to the hotly debated issue of cortical neurons acting as coincidence detectors or temporal integrators (Softky, 1993a). If the flow of signals converging onto cortical neurons is smooth in time, the average level of this input is the only available dynamical variable. In contrast, if cortical neurons act as coincidence
detectors higher order correlation events are necessary to explain, for example, the high CV in the
spike timing (Stevens and Zador, 1998; Softky and Koch, 1993b), the bistability in the sub-
threshold dynamics (Wilson and Kawaguchi, 1996; Anderson et al., 2000), and spike timing
reliability [8]. Thus, systems with a non-vanishing variability in the population activity are a
necessary, minimum requirement for the neuron to act as a coincident detector.

The results presented here demonstrate that, in view of lack of direct experimental
evidence, a rigorous mathematical analysis in combination with available physiological data can
shed light onto a fundamental property of processing in neuronal circuits. Determining a set of
general conditions under which variability must emerge in the population dynamics is an
important step to identify the possible information processing strategies used by the cortex, and
toward an understanding of the compatibility of cortical dynamics with correlation-based
encoding.
Appendix 1

**Proof Lemma 1:** From Theorem 3 we know this is true for the average behavior of the RC-systems. Hence, we must prove that Symmetric Designs obeying the above constraints are indeed behaving as average RC-systems. Considering the parameter $T_f$, we showed in Theorem 3, that, on average, its value does not agree with experimental findings. Nevertheless, its PDF (Probability Distribution Function) has a given width with values along the tails of the distribution that could fit the experimental data. Therefore, it must be shown that Symmetric Designs obeying the above constraints do not lie on the tails of this distribution. Indeed, this is true by definition. Systems on the distribution’s tails must have highly overlapping intervals ($\Delta t_{\text{dec}}$) within and between spike trains (rows, in the binary-strings representation) for any given pair of neurons, therefore having a strong tendency to align spikes along time (columns). Symmetric designs with high CV do minimize these effects, fully exploiting the combinatorial possibilities. Thus, these constrained Symmetric Designs best approximate the average RC-systems. The average behavior of the RC-systems, concerning the free time parameter, $T_f$, can be observed for $N$ or $t \to \infty$. For small time windows of analysis and small $N$, there can be strong deviations from the average. Indeed, under such conditions, it is not even possible to statistically define CV and $c_r$. For the cases under study (durations of $10^5$ ms and $10^6$ neurons) either $N$ or $t$ are high “enough” so that it is possible to fix the CV and $c_r$ parameters. Therefore, in respect to $T_f$, any such a system with well defined high CV and pairwise correlations properties produced by the combinatorial method, behaves as an average RC-system.

The above result is also supported by the *numerical simulation*, which allows a characterization of the convergent behavior of the free-time parameter, $T_f$. As shown in Fig. 3, $T_f$'s variability is higher close to the origin. This simply means that if as few as 3 or 4 cells are considered for a time window as short as 100 ms, the $T_f$ parameter is extremely variable and impossible to define. Nevertheless, its value quickly converges to a stable plateau as soon as the duration or the number of cells used to compute the average, are increased.

*Note:* Given that symmetric designs with high CV are part of the family of objects generated by a random controller, we proved that they are also included in the subgroup of objects which best
represent its average behavior. This is indeed the core of the above demonstration: The incompatibility of the average behavior of RC-systems with the third constraint (i.e., Theorem 3) does not depend on the first two constraints. Imposing them on a zero variability system means to force it to behave as an average RC-system.

**Supplementary Figure 1**

Supplementary Figure 1. Cyclic difference sets. (a) These kinds of Symmetric Designs obey, “in part”, the high CV constraint. The filled circles (spikes) in the bins 2-6-7-9 in the first row represent the initial set. Working with arithmetic mod(13), all the following sets are created by shifting the initial set, thus generating the Symmetric Design. The sum along the rows and columns is constant and equal to four, as shown by the side histograms. IEIs indicate the Inter-Events-Intervals. The histogram of their frequency of occurrence is plotted in panel (b). Here the distribution is almost exponential, except for the “empty bins” as indicated by the arrows. In arithmetic mod(13) results such as 5-8=10 can hold, and, by definition of Cyclic Difference Sets, there won’t be any empty bins. However, it is clear that, for real-time dynamics, this consideration does not make any sense, and the distribution is necessarily incomplete.
High Order Events in Cortical Networks: a Lower Bound.

We pointed out in the Introduction that in order to gain a better understanding of the coding mechanisms used by the cortex to process information, it would be of great advantage to simultaneously record the spiking activity of a very large population of neurons with a millisecond time resolution and a spatial resolution of a single cell. Unfortunately this is still not a feasible experimental technique. Nevertheless, in the previous Chapter we proved that under very general dynamical conditions some degree of fast variability, in the millisecond time scale, must characterize the overall spiking activity of large neuronal populations. In this Chapter we want to solve the key problem of quantifying the magnitude of such fast variability. We use an approach from Combinatorics to find a lower bound for the amplitude of higher order correlation events (HOCEs), in the activity of large neuronal ensembles. The results demonstrate that HOCEs are a natural phenomenon of the cortical dynamics. At the end of the chapter we discuss the implications of the results in terms of coding mechanisms used by the cortex to process information.
2.1 Introduction.

The precise description of the spiking dynamics of large ensembles of neurons at different time scales and spatial resolutions is crucial for a better understanding of the cortical coding mechanisms. As pointed out in the Introduction, examples of key questions to answer are: what is the input dynamics experienced by a typical cortical neuron at the millisecond time scale? Do neurons undergo fast, transient collective synchronizations in their spiking activity? More in general, the study of the cortical dynamics in “natural” conditions is important to explain how the cortex processes information. Theoretical efforts have been made in this direction by Griffith, more than forty years ago, when he first introduced the idea of convergent-divergent chains (Griffith, 1963). Following this scheme, Abeles proposed the well-known model of the synfire chains (Abeles, 1991) whose computational significance has been widely discussed and inspired several theoretical works based on correlated neuronal spiking activity. Conspicuous synchronous firing of a large fraction of cells in the population activity, also referred to as higher order correlation events, plays a key role in all the above mentioned models and theories. We extensively discussed such ideas in the previous Chapter. Unitary events will be the “main actors” in this Chapter too.

Formally speaking, higher order correlation events in the collective behavior of an ensemble of neurons represent short periods of time (few milliseconds) during which a large fraction of cells spike in correlated fashion, with an intensity (absolute fraction of cells involved) and frequency, which is above the by chance level (Grün et al., 2001). We consider, for example, the overall spiking activity of an ensemble of neurons that are spiking according to stationary uncorrelated Poisson processes. This activity would be characterized by a fast Gaussian noise that fluctuates around a baseline level. Thus, once a while, peaks of highly correlated spikes will statistically emerge. Formally speaking, these events, which are a form of fast, high-amplitude “noise”, cannot be considered HOCE. In this Chapter, relaxing a bit the definitions and having no a-priori assumptions about the underlying statistical processes we will denote with HOCE any form of highly correlated activity which is higher than the pairwise correlations. In what follows, we will use the terms HOCE and “high-amplitude fast variability” equivalently, as if they were...
synonymies. Next, we will face the challenging problem of defining a lower bound for the unitary events.

Using an approach related to Combinatorial analysis, we will prove that under very general dynamical conditions, the magnitude of HOCE is such that they must be considered a natural phenomenon of the cortical dynamics. The implications in terms of neuronal computation will be extensively discussed in the Conclusions.

To prove this result we will use the same three general dynamical constraints, as introduced in the previous Chapter, which are well-known dynamical properties of the single cell and pairs of cells' activity. C1: The single cell spike timing variability is very high. The standard deviation of the inter-spike intervals over their mean, i.e. the CV, assumes values close to one, suggesting that the spike timing statistics can be described by a Poisson process (Softky and Koch, 1993). C2: Pairs of cells sharing similar orientation properties tend to synchronize their activity (Usrey and Reid, 1999). Correlation analysis produces cross-correlograms of pairs of spike trains with central symmetric peaks, which are occasionally associated to satellite peaks signaling the presence of oscillatory activity. C3: Correlations have also been detected between pairs of cells in the subthreshold domain (Lampl et al., 1999; Stern et al., 1998). The available data indicate that, on average, pairs of neighboring cells correlate their subthreshold membrane potential dynamics for as long as 40% of the time, with peaks as high as 80%. Sensory stimulation can further increase this fraction of shared temporal variability.

We also briefly recall some of the definitions introduced in the previous Chapter, which are important for the present discussion too. Weak pairwise correlations between spike trains are quantified as the ratio of the peak amplitude over the offset (baseline) of the spike trains' cross-correlograms, i.e. the Relative Modulation Amplitude (RMA) (König, 1994). Instead, the values of the subthreshold correlations are quantified using the amplitudes of the normalized peaks of the crosscorrelograms between pairs of subthreshold traces (Lampl et al., 1999), and, again, for Higher Order Correlation Events, we mean here synchronous spiking episodes occurring in neuronal assemblies containing more than two cells (triplets, quadruplets, etc...)\(^1\).

\(^1\) To help the reader who is just interested in the logic structure of the Chapter, and wants to skip the details of the mathematical formalism, we used the following strategy: In several parts of the Chapter we put summarizing paragraphs that describe what done so far and what is going to follow. They begin with a bold “Summary” and are ended by a “•” symbol.
2.2 The lower bound of PSTH variability

Summary: Before defining the mathematical details of the model, we want to schematically outline the logic structure adopted in the following. We start introducing what we call the “Combinatorial Method”, which allows us to describe in simple mathematical terms the spiking activity of a large ensemble of cells. A key property implemented in the algorithm, is its ability to generate systems (i.e. large ensembles of spike trains) whose HOCE’s magnitude underestimates those of cortical networks, thus representing what we call a “lower bound” (Section 1A-B).

We want to briefly comment on a very natural objection that might arise following the above outline: How large groups of spike trains that underestimate the fast cortical variability can be generated, if the fast cortical variability is unknown and is exactly what we are looking for? This point, rather than being a logic contradiction is a central part of the Chapter and the answer will become clear following the derivations until Lemma 2 of Section 2.2.B.

In the following section we introduce the details of the Combinatorial Method.

A. The Combinatorial Method: describing the building block.

To give an easy intuition of what kind of systems the Combinatorial Method can generate (CM in the following), it helps to consider raster plots as a representation of the dynamics of a large group of spike trains. Simplifying, the CM can be considered as a raster plot generator with some “special features”. Raster plots can also have a binary representation in the following way: let’s consider an empty matrix with as many rows as the raster plot (i.e. the total number of cells) and as many columns as the total time duration of the raster plot divided by the time resolution used to generate the raster. If the occurrence of a spike by a given cell at a given time in the raster is represented in the matrix by a ‘1’ in the corresponding row and column, and the non-occurrence by a ‘0’, then the whole population’s dynamics can be associated to a binary matrix where each row is a binary string associated to a given spike train (Rieke et al., 1997). The aim of the CM is to create a large group of binary strings (of the order of $10^5$) respecting the constraints of weak pairwise correlations and CV, i.e. C1-C2, and, at the same time, minimizing the higher order correlation events. In this binary scheme, HOCE are simply “large” vertical alignments of ‘1’ s along the columns of the binary matrix.
A key property implemented in the CM is the exploitation of the combinatorial possibilities in distributing ‘1’s between the bins of the binary matrix, in such a way that C1-C2 are satisfied and the magnitude of HOCE is minimized.

We now describe few simple examples and implement such a binary matrix. The starting point is to create an arbitrary binary string with a fixed given number of ‘1’s (i.e. fixed firing rate), that respects the constraint of refractoriness and high CV. This means that the spikes cannot occur too close each other and their distribution in time is according to a Poisson process. The next step is to create a second strings that respects not only the constraints about refractoriness, high CV (C1), and fixed rate, but also the C2 constraint. This implies that a given small fraction of ‘1’s in the first and second string must occur in the same columns (weak pairwise correlations). The following step is to generate a third string satisfying C1 as well, and with a distribution of ‘1’s along the columns such that the pairwise correlation constraint is satisfied not only for the pair of strings 1-3, but also for the pair 2-3, while leaving the correlation properties of the pair 1-2 unchanged. This way all the three strings have weak pairwise correlations with each other. This must be done minimizing the occurrence of HOCE, which means that the maximum counting of ‘1’s per every column is two (pairwise correlations) and triplets (vertical alignments of three ‘1’s in the same column) are not formed. This procedure cannot go on forever and, after creating a certain number of strings, we will eventually run out of combinatorial possibilities due to the limited number of ‘1’s that can be used, and accordingly triplets will emerge. With increasing number of strings then quadruplets will be formed as well, and so on. The largest group of strings that satisfy the C1-C2 constraints and that is characterized solely by pairwise correlations, without any triplet, defines what we call a block of order two. An example of these ideas, in a raster plot representation, is show in Fig. 1(a-b). Fig. 1(a) shows a block of order two for a given rate and pairwise correlation strength, while Fig. 1(b) shows a block of order three that still satisfies the constraint of weak pairwise correlations with all the spike trains in the block of order two. Fig. 2(a-b) shows another example referred to a well-studied system in the field of Design Theory, the Fano plane. This example is particularly interesting in relation to the previous Chapter, where Symmetric Designs have been introduced. Each filled circle in the figure indicates a spike in the raster plot representation, or a ‘1’ in the binary matrix representation. Each row is associated to a spike train. Every box represents a time bin whose duration is related to the time resolution of the system. Empty boxes indicate absence of spikes in
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the corresponding time intervals. In this way, as also explained before, the whole plot can be associated to a binary matrix and equivalently to a raster plot. For the reader who got interested in Design Theory after reading the previous Chapter, this example shows how the Fano Plane and more in general any zero variability systems like the Symmetric Designs, can be though of as generated by the CM through a "sum" of blocks of different orders.

**Figure 1.** Combinatorial method: (a) Example of a $P_{5,2}$ system. The letters on the top indicate the best combinatorial choices to respect the C1 and C2 constraints: ‘f’ guarantees pairwise correlations between cells 2-4, ‘d’ between cells 1-3, ‘e’ between cells 1-4 and so on. Four is the maximum number of trains allowed by the
combinatorial possibilities. When other cells are introduced according the preceding rules for the pairwise correlations, the vertical alignment (still constant through all the bins, as shown by the bottom histograms) increases up to a value of three ($\text{order}=3$), (b). Here, the numbers on top of the spike trains indicate the possible combinatorial strategies to guarantee pairwise correlations with the block of cells in the above panel. For example, the four spikes in cell number 7 (labeled with the number ‘3’) are combined with the trains $d_3$ (for correlations with cells 1-3) and $f_3$ (for correlations with cells 2-4) in the top panel. In this way pairwise correlations with all the cells in Fig. 1(a) are established for cell number 7 and two more spikes (indicated in dark gray) are available to create pairwise correlations with the remaining cells (5 and 6) within the same block.

We want now to quantify the ideas presented above, by introducing a formalism taken from Probability Theory and Combinatorics. This formalism will help us to define systems characterized by the properties described in the Introduction, i.e. large groups of spike trains whose HOCE’s structure underestimates the fast cortical variability.

We denote with $P_{m,n}$ the maximum number of binary strings, containing $n$ ‘1’s each (or $n$ spikes), and $n_0$ intersections (of ‘1’s) between any pair of strings. $r$ denotes the maximum number of ‘1’s aligned in time, what we called the order of the block in the above examples. Using for example this formalism for the block of order $r=2$ of the Fano Plane in Fig. 2(b), the parameters would be set as follows: $n=3, n_0=1,$ and $P_{2,}^2 = 4$. When the maximum number of strings is created for a given order, then the population PSTH (the total sum of the filled circles per each column in the block of order $r$) is, by definition, constant and equal to $r$. In Fig. 1(a-b) this histogram has been explicitly plotted at the bottom of each raster. In the example shown in Fig. 1(a), $n_0=2, n=6,$ and $r=2$. More in general, for the block of order two the following relationship holds true: $P_{m,n}^2 = \text{floor}\left(\frac{m}{n_0} + 1\right)$. As shown in the example, after $P_{2,}^2 = 4$ strings, there are no more combinatorial possibilities and the problem is mapped to a higher order. We denote with $S_{m,n}$ the sub-block of strings of the block $P_{m,n}$, which “causes” the transition from the order $r-1$ to $r$, being $r$ any positive integer greater than one. More explicitly, as shown in Fig. 2(b), $S_{1,}^3 = 3$, and this sub-block is made by rows 5, 6 and 7. Indeed, the first four rows generate a block whose PSTH (i.e. the total sum along each column) is constantly equal to 2. Including rows 5, 6, and 7 causes the transition from the order 2 to the order 3.
Figure 2. Symmetric Designs: (a) Representation of the Fano plane, projective plane of order 2, or symmetric (7,3,1)-design. The numbered vertices form triplets that can be associated to a "raster-matrix" of spike trains where the filled circles would indicate spikes and the width of each column a time step proportional to the time resolution used to get the raster plot, (b). A property of the Fano plane and of the raster plot it represents, is that the number of elements (filled circles or spikes) along the columns is constant and equal to the number along the rows. The thick horizontal line separates the order 2 from the order 3. Summing along the columns above the thick lines gives a constant counting =2 (order), while summing below it, gives a constant value =3. The complete structure gives a constant total counting of three for every column i.e. a flat population PSTH.

Concerning the order of the sub-blocks, it is possible to prove the following results:

**Theorem 1:** In a system created by the combinatorial method, the following inequality between sub-blocks must hold: \( S_{m,n}^{r+1} \leq S_{m,n}^r \)

**Proof:** Every time a new block is added, the number of available '1's, \( n' \), to create internal correlations within the spike trains of the new added block, is lower than in the initial case since a non-zero fraction of "ones" in the \( r + 1 \) sub-block are "frozen" for the correlation constraints with the \( r \) sub-block (This is shown in Fig. 1(b) by the dark gray spikes). The number of unconstrained elements, \( n'' \), in the \( r + 1 \) sub-block is lower than in the \( r \) sub-block. Since the number of possible trains per sub-block is proportional to the combinations \( \binom{m'}{n'} \), with \( n'' < n' \), then \( S_{m,n}^{r+1} \leq S_{m,n}^r \). The equality can hold when the number of available spikes is much higher than \( n'' \).

To give an easy intuition of this Theorem, looking at Fig. 2(b), the sub-block of order \( r+1=3 \) has 3 elements, i.e. rows 5, 6 and 7, while the sub-block of order \( r=2 \) has 4 elements, i.e. rows 1, 2, 3 and 4. A similar example is given in Fig. 1(a-b).
B. Generality of the combinatorial method.

Summary: Before introducing other Theorems and Lemmas, we want to summarize what done so far and outline what is going to follow.

The CM is a statistical method to generate spike trains, which is based on the combinatorial possibilities to distribute spikes over time, in such a way to respect the C1-C2 constraints of the dynamics. By introducing an appropriate formalism, it is possible to define a "special ensemble" of spike trains created by the CM, which is the largest group (block) of spike trains, characterized solely by pairwise correlations (order two), but without triplets or any HOCE.

In the following we are going to show how blocks of order two can be used as "building blocks" to create larger groups of spike trains whose HOCE's structure underestimates the fast cortical variability. The third constraint, C3, is going to play a very important role in the following derivations. We use it now to prove the following lemma.

Lemma 1: For a group of spike trains created by the CM, the maximum and minimum fraction of time during which two cells can be correlated, are given by

\[ T_f = 1 + \Delta_{dec} \times (c_s - 2) \quad \text{and} \quad T_u = f_{corr} \times (c_s + 2) - 2 f_{dec} \times \Delta_{dec} \]

Proof: The proof follows step by step the proof of Theorem 3 in the previous Chapter, with the important difference that the starting equations are determined by the CM and not by the RC Method. Because of that, the analytical derivations have a completely different form. Since the constraint C1 about high CV is respected, the time between two spikes can be set to \( ISI = \frac{1}{f} \) and the time between two correlated spikes in a pair of neurons to \( T_c = \frac{1}{f \Delta_{cs}} \). This way the starting equations are

\[ T_f = \frac{ISI - 2 \Delta_{dec} \times \Delta_{defcs}}{ISI} \quad \text{and} \quad T_u = \frac{2 \Delta_{corr} - \Delta_{dec} - \Delta_{defcs}}{ISI} \]

The result comes simply by working out the mathematics as done for Theorem 3 in the previous Chapter. 

This Lemma allows us to prove a very important result to demonstrate that using the CM it is possible to create systems that underestimate the fast cortical variability, even if we do not know what the cortical variability is.
Lemma 2: The population-PSTH’s variability of any block produced by the Combinatorial Method, which obeys the constraints of weak pairwise correlations and high CV (C1-C2), is an underestimation of the fast cortical variability.

Proof: Also for this proof we refer to the discussion following Theorem 3 in the previous Chapter, keeping in mind that the analytical form of the equations is completely different since different algorithms (CM here, RC in the previous Chapter) are used to generate spike trains. Using the results of Lemma 1, we plot in Fig. 3 the dependence of $T_u$ and $T_f$ (quantifying the lower and upper tails of the distribution of the subthreshold correlation strengths, see previous Chapter) on the set of parameters ($\Delta_{corr}, \Delta_{dec}, f, C_v$), and we check if there is ever compatibility with reported experimental values (C3). When $f \geq 30$ Hz (we are interested in high input regimes), $\Delta_{corr} > 10$ ms (reported values are around 40 ms (König et al., 1995)) and $\Delta_{dec} \leq 5$ ms (in the range of absolute-relative refractoriness), it is not possible to obtain values of $T_u$ and $T_f$ compatible with the physiologically observed distribution of the subthreshold correlation strengths (C3), Fig. 3.

![Figure 3](image_url)

Figure 3. This figure corresponds to Fig. 2(d) in the previous Chapter, here derived for the Combinatorial Method. The three panels show the behavior of $T_f$ and $T_u$ as a function of $\Delta_{corr}$ for three different values of the mean firing rate: 30, 60, and 80 Hz respectively. The five different horizontal and oblique lines refer to $T_f$ and $T_u$ respectively, while $\Delta_{dec}$ changes from 1 to 5 ms (1 for the top lines and 5 for the bottom lines). The thick vertical line indicates a typical $\Delta_{corr}$ value for pairwise correlations in the spiking activity (10 ms, much shorter than for subthreshold correlations, which has been found to range around 40 ms). The thick horizontal line indicates the mean value for the distribution of the subthreshold correlation strength as found in Lampl et al. 1999.

This important result about the incompatibility of the CM and the constraint C3 is not a proof of Lemma 2 since incompatible does not mean lower. To prove the correctness of the Lemma, we are going to show that the source of incompatibility has to be found in the “combinatorial nature”
of the algorithm. Indeed, as stressed many times above, the CM maximally exploits the combinatorial possibilities in distributing the spikes, so to minimize the HOCE. This very “sparse” (but not random) distribution in time of the spikes, during high input regimes, is what causes the disagreement with C3. We show now that, as soon as some degree of temporal alignment is allowed, the third constraint is satisfied.

We use a numerical simulation to illustrate this point:

**Numerical Simulation**: We refer here to the results of the numerical simulation as shown in the previous Chapter (Fig.3). Leaving the details to the previous Chapter, we recall here the underlying rational. Two systems are compared: uncorrelated Poisson spike trains and a group of spike trains with some degree of HOCE. The $T_f$ parameter agrees with experimental data only in the latter case. Important features of the simulation are the high variability observed close to the origin of the plot and the asymptotic behavior. As long as the number of cells in the ensemble is larger than 3 and the time window is longer than 100 ms, $T_f$ reaches a stable convergent value. Thus the results found do not critically depend on the size of the block.

The results of the simulation confirm that the source of incompatibility between the CM and C3 is the “pathological” absence of temporal alignments for all those systems produced by the CM. Some increased level of HOCE is required to enter in a physiologically plausible range.

**Summary**: The proof that CM underestimates the fast cortical variability, (even if we do not know the magnitude of the cortical variability) has been obtained by considering a consequence of the “extremely low” degree of HOCE in systems produced by the CM, i.e. the incompatibility between CM systems and the C3 constraints. When this built-in property of the CM to generate zero variability systems is removed by allowing some degree of temporal alignments between the spikes, the compatibility with C3 is recovered.

In the following we are going to use this result to create an arbitrary large ensemble of spike trains that underestimates the fast cortical variability. As anticipated before, the underlying idea is to use blocks of strings of order two, i.e. subgroups of spiking neurons characterized by a flat population PSTH in the few tens of milliseconds time scale, as building blocks to create large scale systems with a negligible high order correlation structure, thus defining the lower bound we are looking for.
C. A lower bound for the unitary events in the cortical dynamics.

Considering a non-zero variability system, created as the sum of several 2\textsuperscript{nd} order blocks, as described above, we make the following assumptions: instead of imposing that any two strings (spike trains) in the system have the same correlation strength, we simply require that the strings in the same 2\textsuperscript{nd} order block are correlated according to a given \( n_{\omega} \) parameter, while, for the correlations between the blocks, we require a lower level of the correlation strength, according to a new parameter \( n_{\omega'} << n_{\omega} \), which should be set to a small non-zero integer value (\( \geq 1 \)). It is important to stress that this is a strong simplification also in respect to electrophysiological data. Indeed, the parameter \( n_{\omega'} \) represents a sort of “decorrelation” factor between the blocks, in the sense that it strongly reduces the previously assumed weak pairwise correlations within the blocks. This forces the average correlation strength to assume lower values than those physiologically observed. It is now possible to formulate the following:

**Theorem 2**: A step function, of step size \( P_{m,n_{\omega}}^{2} \), is a lower bound for the higher-order events in the population dynamics.

**Proof**: Given an initial block with as many as \( P_{m,n_{\omega}}^{2} = \text{floor}(\frac{n_{\omega}}{n_{\omega'}} + 1) \) strings, the size of the following block is lower than, or equal to, the size of the first block (Theorem1) and, being a built-in property, the order \( r \) must increase at least by a factor of one. Each block represents a zero-variability system that cannot be associated to a cortical dynamics, as in Lemma1. This means that every block carries an *intrinsic* underestimate of the cortical variability. When more blocks are added together, there is again an underestimation of the fast cortical variability, but this time coming from an *extrinsic* source, i.e. \( n_{\omega'} << n_{\omega} \), as in the assumptions. Indeed, we let the order \( r \) increase only by a factor of one every time a block is added (i.e. the minimum possible increase given non-zero pairwise correlation strengths). As shown in Fig. 4(a), by always using 2\textsuperscript{nd} order blocks it is possible to get a step function of step-size \( P_{m,n_{\omega}}^{2} \), which relates the number of strings in the system to the order \( r \). This step function is produced accordingly to constraints that carry *intrinsic* and *extrinsic* underestimates of the cortical variability, thus defining a lower bound. ■
Figure 4. Lower bound. (a) Step function indicating the relationship between the total number of cells in the network and the order for the correlated unitary events in the lower bound condition ("r" in the text). The dotted line is the linear fit of the step function. This specific example relates to the schematic in Fig. 2(a-b). (b) Schematic of the different estimates for the higher order events produced by the different methods. The shaded area represents the part of the plane where systems with variability necessarily lower than the cortical one can exist (see text). The total number of neurons is related to the order of the events via a linear relationship, with slopes changing in accordance to the generating method: P, Poisson; Co, Combinatorial. The line for the Combinatorial method is derived by linear interpolation of the step function as in Fig. 3(a) and is well within the shaded area. The “real” lower limit (LL) is somewhere above it and it has been associated to a linear behavior just for simplicity. The variability of the cortical dynamic dominates the upper part of the plot, well above the Co-lower bound. (c) Variability of the PSTH in the lower bound condition; since the integral of the PSTH is kept constant, a positive peak deviation (+ sign) of the 160% from the Poisson Background (PB) must be associated to an equivalent negative peak (- sign), inducing a preponderant global variability. The PB is normalized to ‘1’ for simplicity.

Note: This result does not depend on the choice of initializing the combinatorial method with a block of order two (see the Numerical simulation above). Indeed, reconsidering the example of Fig. 1(a), the size 4 of the step function is $P_{4,3}^2$. Using a step larger than $r=2$ would have lead to different conclusions about the lower bound, as for $P_{4,2}^3 > P_{4,3}^2$. For example, $P_{4,1}^3$ (the Fano plane)
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gives a step=7. What matters for the present analysis is that, if pairwise correlations are considered, it is not possible to go below the order two. Note that the "slope" of the step function obtained with $P_{m,n}^2$, might not be the steepest one! Fig. 4(b). Even a step with decreasing length, as it would be natural to consider from Theorem 1, would also produce a steeper behavior. That is why it is more correct to talk about a lower bound and not about a lower limit.

Next, we will show, using very realistic numbers taken from physiological experiments, that the magnitude of HOCE, emerging in this lower-bound condition, is much higher than the magnitude of HOCE observed in a system of uncorrelated Poisson spike trains, with identical second order correlation properties (Fig. 4(b-c)). Uncorrelated Poisson spike trains are used here as a sort of “reference level” to quantify the properties of the HOCE in an ensemble of spiking neurons.

**Summary:** The logic of the following paragraphs can be summarized in this way: From Lemma 1 and 2, we know it is possible to generate a large group of spike trains that underestimates the fast cortical variability, and that are compatible with the C1-C2 dynamical constraints. Next, we quantify the magnitude of HOCE in such systems produced by the CM in the lower bound condition, and use uncorrelated Poisson spike trains as a reference level. The results will show that, given the remarkable magnitude of HOCE in the lower bound conditions, unitary events must be considered a central feature of the cortical dynamics.

In the following Section we carefully quantify the comparison between uncorrelated Poisson systems and spike trains in the lower-bound condition, using both a numerical and an analytical approach.

**D. Variability in the lower-bound condition.**

Considering the raster plot representation of the dynamics of a group of spiking neurons, the time axis can be subdivided into a given number of bins, $N_{bin}$, whose length is determined by the time resolution, $\Delta t_{bin}$ (as explained for the binary matrix). If uncorrelated Poisson processes generate the spike trains, the average number of spikes per time bin is given by $\frac{N_t}{N_{bin}} \times N_m$, with $N_m$ being the total number of strings. Instead, if the group of spike trains is a sum of second order blocks, as in the lower bound conditions, it is possible to obtain a linear relationship between $N_m$ and the order $r$ of temporal alignments (magnitude of HOCE) by interpolating with a line the step-
function described before (Fig. 4(a), broken line). Then, the order \( r \) for the Poisson and lower bound condition is the same, when the following equation is satisfied:

\[
\frac{1}{\text{floor}(\frac{n_e}{n_0} + 1)} \times N_m + 2 = \frac{n_e}{N_{bm}} \times N_m; \quad \text{eq}(1)
\]

Working out the mathematics and making few simplifications (i.e. omitting the "floor" function and considering that \( \frac{n_e}{n_0} \gg 1 \)), the equation does have solutions iff \( n_0 \times N_{bm} < n_e \). As pointed out before, we are interested in correlations during high input regimes, therefore, using 35 Hz for the average firing rate, \( c_s = 0.1 \) and \( \Delta t_{bin} = 1 \text{ms} \) for a 1 sec. time window of analysis (which leads to \( N_{bm} = 1000 \)), the equation has no solution. This does not depend on the window size, as can be proved by changing the variables \( n_e = \langle f \rangle \times N_{bm} \times \Delta t_{bin} \) and \( n_0 = \langle f' \rangle \times N_{bm} \times \Delta t_{bin} \), with \( f = f / 10 \) since we fixed \( c_s \) to 0.1. \( N_{bm} \) then cancels out in the inequality and it can be rewritten as

\[
\langle f \rangle > 1/(10 \times \Delta t_{bin}),
\]

which is satisfied only for an average firing rate above 100Hz. Even considering only groups of cells being optimally activated (\( \langle f \rangle = 80 \text{Hz} \)), the equation has still no solutions. This means that in the correlated (lower bound) case, there must be vertical alignments (HOCE) of larger amplitude than in the uncorrelated Poisson situation. An estimate of such magnitude can be obtained by using the above numbers and \( N_m = 10^4 \). The fractional difference between the orders in the two ensembles of spike trains is 160%. Since the total number of spikes in the two groups is the same, the integral of the corresponding population PSTHs is equal, and a 160% average increase in the order \( r \) for the lower-bound condition, in respect to the "Poisson background", implies the existence of high amplitude, sharp peaks in the population PSTH, i.e. HOCE of high magnitude for the lower-bound condition (schematic in Fig. 4(c)). The percentage is still "high" even for the extreme case of a much smaller, highly responsive population of neurons, giving a fractional increase of 22% when using \( N_m = 300 \), \( n_0 = 8 \), \( n_e = 80 \). The relative independence of the fractional increase from the parameter \( N_m \) is due to the fact that for typical values of the parameters \( \frac{N_m \times n_e}{n_0} \gg 2 \), then \( N_m \) can be cancelled out in eq(1). Instead, the absolute magnitudes predicted for the peak’s amplitudes in the population PSTHs (the magnitude of the HOCE or the order of the system) are strongly dependent on the precise value of \( N_m \), ranging from 911 to 29, for \( N_m \) equal to \( 10^4 \) and 300 respectively.
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The two methods, Poisson and Combinatorial, can be compared analytically in two ways: First method: due to the pairwise correlations, the building block of the step function, $P_{n,m}^2$, has an order, $r = 2$, which is higher than the order of an uncorrelated Poisson system with an equal number of spike trains. Indeed, considering that for the Poisson case $r = \frac{n_t \times N_{in}}{N_{bin}}$ and using $N_{in} = \frac{n_t}{n_o} + 1$ (omitting the floor function), changing the variables as done before, then

$$r = (\langle f \rangle \times \Delta t_{bin}) \times (c_s^{-1} + 1),$$

which can be higher than 2 only for firing rates higher than 200 Hz.

Second method: considering the $(N_m, r)$-plane as in Fig. 4(b), all the systems characterized by an order $r$ lower than the order of systems produced by the CM, must be characterized by functions whose plot remains below the lower bound line. This trivial graphical observation can be quantified. A linear relationship between the total number of neurons in the population and the order of the vertical alignments in the population PSTH, $r$, can be computed for both the Poisson and the Combinatorial method. For the Poisson case we showed before that

$$r = \frac{n_t}{N_{bin}} \times N_m,$$

and given that $n_t = \langle f \rangle \times N_{bin} \times \Delta t_{bin}$, then $r = \langle f \rangle \times N_{in} \times \Delta t_{bin}$. For the combinatorial approach, omitting the floor function and using the same expression as above for $n_t$, we get $r = \left( N_{in} \right) + 2$. Using $N_{in} = 10^4$, $c_s = 0.1$, $f = 35$ Hz, and $\Delta t_{bin} = 10^{-3}$ sec, we obtain for $r$ the values 350 and 911, for the Poisson and Combinatorial methods respectively. These results are schematically shown in Fig. 4(b).

For the duration and frequency of occurrence of these events (two non-independent factors since the PSTH integral is constant) it is possible to make general statements referring to Fig. 1(a-b). Given a spike train, all its spikes can be possible points in time to generate HOCE in the population’s activity. Since the spike trains are generally only partially overlapping, but never non-overlapping (C2), it is reasonable to expect $\left[ \langle f \rangle \times 2 \times \langle f \rangle \right]$ as a range for the frequency of occurrence of the unitary events. Moreover, since the peaks in the population PSTHs, associated to these points in time, can be considered also as the “generators” of the pairwise correlations (Bothé et al., 2000; Brunel and Hakim, 1999), their duration is related to the width of the
experimentally measured cross correlograms, i.e. few tens milliseconds (Amit and Brunel, 1997b).

Summarizing, the lower bound condition underestimates, by definition, the impact of unitary events in the dynamics of neuronal ensembles. So the fast variability in the population PSTHs, associated to HOCE, must be much stronger if experimentally measured in cortical networks, as proved by Theorem 2.

2.3 Conclusions.

The problem addressed in this study is to characterize the temporal dynamics of large ensembles of neurons in the millisecond time scale during so-called high input regimes. We used a simple theoretical approach: Given that direct experimental data is not available, we used well-known and very general electrophysiological results as constraints (C1-C3) of the population’s dynamics. Dynamical systems obeying such constraints cannot behave in any general possible way. C1-C3 can “confine” the neuronal dynamics to specific sub-spaces in the highly dimensional space of the dynamics. We then focused on a special type of systems, generated by what we called the Combinatorial Method. A key property of these systems is their compatibility with the constraints C1 and C2, but not with C3. This is due to their built-in property of maximally exploiting the combinatorial possibilities when generating the spike timings, in such a way to induce pairwise correlations, high CV, and at the same time, minimizing the occurrence of HOCE. We proved that these systems underestimate the fast cortical variability thus defining a lower bound for the magnitude of cortical unitary events. When comparing quantitatively CM systems with uncorrelated Poisson spike trains (used as reference level) we found that higher order correlation events are a natural phenomenon of the dynamics. Since the CM produces underestimates of the higher order correlations, it follows that the relevance of HOCE must be even more significant in cortical networks.

Concerning the importance of these results in terms of computation, synchronous events (HOCE) appeared in the theoretical discussion since 1963 with Griffith (Griffith, 1963) and kept on attracting more and more interest through the years. In theoretical and experimental studies they have been labeled with the term “surges” of activity, “higher order events”, “volleys”, “barrages” of inputs, “conspicuous coincidences”, “unitary events”, “population spikes”, or “large brief excitatory events” (Bothé et al., 2000; Grün et al., 2001; Stevens and Zador, 1998;
Abeles et al., 1993; Abeles, 1991; Amit and Brunel, 1997a; Martignon et al., 1995; Loebel and Tsodyks, 2002).

Despite the fact that they have never been observed due to technical limitations or deduced theoretically in an undisputable way, synchronous events in the cortical dynamics have been the central topic of several studies analyzing their relevance in relation to information coding. Assumed to exist in “synfire-chains” (Abeles, 1991), they are meant to have a dynamical impact not only at a network level, but also at the cellular one, in respect to the long lasting dispute of “coincidence detector” vs “pure integrator” for the neuronal modality of input processing, e.g. (Softky and Koch, 1993). In conclusion, this work provides a formal demonstration that unitary events must appear in the constrained population dynamics, to an extent that is related to the computed lower bound. This theoretical analysis provides not only a formal description about how information flows in cortical networks, but strongly supports coding strategies based on correlation schemes. Advances in recording techniques are needed for a final experimental validation.
Chapter 3

Two-state membrane fluctuations driven by weak pairwise correlations

In these last two Chapters, we shift the attention from the network level to the cellular one. We want to analyze how the results found in Chapter 1 and 2, about the dynamics of HOCE, can affect the single cell response properties.

More specifically, this Chapter demonstrates the existence of a link between two well-known phenomena, described at the network and single-cell level respectively: (1) Physiological experiments demonstrate the existence of weak pairwise correlations of neuronal activity in mammalian cortex (Singer, 1993). The functional implications of this correlated activity are hotly debated (Roskies et al., 1999). Nevertheless, it is generally considered a widespread feature of cortical dynamics. (2) In recent years, another line of research has attracted great interest: the observation of a bimodal distribution of the membrane potential defining up- and down-states at the single cell level (Wilson and Kawaguchi, 1996; Steriade et al., 1994; Contreras and Steriade, 1995; Steriade, 2001). Here we use a theoretical approach to demonstrate that the latter phenomenon is a natural consequence of the former. In particular we show that weak pairwise correlations in the statistics of the inputs to a compartmental model of a layer V pyramidal cell can induce bistability in its membrane potential. We illustrate how this relationship can account for the observed increase of the power in the $\gamma$-frequency band during up-states, as well as the increase in the standard deviation and fraction of time spent in the depolarized state (Anderson et al., 2000). In order to quantify the relationship between the correlation properties of a cortical network and the bistable dynamics of single neurons we introduce a number of new indices. Subsequently we demonstrate that a quantitative agreement with the experimental data can be achieved introducing voltage dependent mechanisms in our neuronal model such as $\text{Ca}^{2+}$ and $\text{Ca}^{2+}$ dependent $\text{K}^+$ channels. In addition, we show that the up- and down-states of the membrane potential are dependent on
the dendritic morphology of cortical neurons. Furthermore, bringing together network and single cell dynamics under a unified view allows the direct transfer of results obtained in one context to the other and suggests a new experimental paradigm: the use of specific intracellular analysis as a tool to reveal the properties of the correlation structure existing in the network dynamics.

3.1 Introduction

In this study we address the relationship of two experimentally observed phenomena: At the network level, correlated spiking activity between ensembles of neurons has been described in recent years. At the cellular level, the observation that the membrane potential dynamics of single neurons can show distinct up- and down-states has received a lot of attention.

Regarding the first phenomenon, multi-electrode recordings in cat visual cortex have demonstrated that pairs of neurons sharing similar orientation tuning properties tend to have synchronized spiking activity (Singer, 1993). This finding has been confirmed in different species (Bair, 1999) and different cortical areas (Salinas and Sejnowski, 2001). The synchronization pattern is dependent on the properties of the stimulus. For example, in case coherently moving gratings or randomly moving dots are used as visual stimuli they elicit cortical activity that displays pairwise correlations of different degree (Usrey and Reid, 1999; Gray et al., 1990). Moreover, cross-correlation analysis shows that rather than having a precise synchronization, optimally driven neurons lead over sub-optimally driven ones (König et al., 1995a) (Fig. 1b). This suggests that under realistic conditions, cortical dynamics is highly structured in the temporal domain (Roskies et al., 1999).
Figure 1.

Model neuron and the temporal structure of its input. a, Reconstructed layer 5 pyramidal cell (left) with a schematic of five input spike trains sharing weak pairwise correlations (right). For every pair of spike trains there are moments in time when the probability of firing together is high and pairs of synchronized spikes occur. Due to the high level of input-convergence higher-order events emerge statistically, and are shown as triplets in the example (Benucci A. et al. in preparation). b, Cross-correlation analysis of paired extracellular recordings from cat area 17 while using moving bars as visual stimuli (data taken from König et al. 1995). The peak size is proportional to the strength of the correlation. The shift of the peak indicates a phase-lag of the firing of one neuron relative to the other. In general, optimally driven cells tend to lead over sub-optimally driven ones. Solid line, Gabor-fit for parameters estimation. c, Cross-correlogram of the synthetic data. Solid line, Gabor-fit of the cross-correlogram.

The impact of a large number of randomly timed or synchronized inputs on the subthreshold dynamics of single neurons has been studied in simulations (Salinas and Sejnowski, 2000; Bernander et al., 1994b; Destexhe and Paré, 1999; Shadlen and Newsome, 1998; Softky and Koch, 1993). However, taking into account our current knowledge of the correlation structure of cortical activity, we have little insight into the cellular dynamics under realistic conditions (Singer, 1993; Lampl et al., 1999; Douglas et al., 1991; Stern et al., 1997; Agmon-Snir and Segev, 1993; Mel, 1993; Destexhe and Paré, 2000; Singer and Gray, 1995).
Regarding the second phenomenon, a number of intracellular studies have shown, that the membrane potential of neurons does not take on any value between rest and threshold with equal probability but rather that it assumes either a depolarized state, associated with spiking activity, or a resting state where the cell is silent (Figure 2a,b right panels). This behavior has been observed in different animals and brain structures (Anderson et al., 2000; Stern et al., 1998; Steriade et al., 2001). This bi-stability of the membrane potential is referred to as up- and down-states and its biophysical properties have been characterized (Wilson and Kawaguchi, 1996; Lampl et al., 1999; Douglas et al., 1991; Stern et al., 1997; Lewis and O'Donnell, 2000; Wilson and Groves, 1981; Kasanetz et al., 2002) (Figure 2a,b right panels). The origin of up- and down-states has been related to pre-synaptic events (Wilson and Kawaguchi, 1996), however, the underlying mechanisms are currently not identified.
Figure 2.

Intracellular somatic recordings. a, The membrane potential of the model neuron is shown during optimal stimulation (left panel). Spiking episodes (burst-like behavior) are associated with the depolarized states of the membrane potential (up-states). Following spiking activity, there are periods in which the simulated cell is...
in a more hyperpolarized state and silent ("down-states"). The pairwise correlation strength of the input spike trains has been set to 0.1 and the mean input firing rate to 85 Hz, the alternation between up- and down-states has also been found in several experimental studies using intracellular recordings (right panel). b, Histogram of the distribution of the membrane potential recorded under the conditions as shown in (a) after removal of the action potentials. The membrane potential does not take any value between the up- and down-states with equal probability but the histogram shows 2 peaks (left panel). Similarly, the biphasic behavior in the membrane potential has been experimentally observed (right panel). C. If the cell in the simulation is stimulated solely by uncorrelated background activity (6 Hz), the bimodality disappears (left panel). The corresponding trace of the membrane potential is shown in the inset. Similar "shapes" in the histograms of the membrane potential under similar stimulation conditions have also been observed experimentally (right panel). Please note, that when not using visual stimulation Anderson et al. (2000) found bimodal as well as non-bimodal distributions of the membrane potential. A non-bimodal example is shown here (see also discussion). d, The duration of the up-states has been increased ten times in respect to Fig. 2a due to the introduction of Ca\(^{2+}\) and Ca\(^{2+}\)-dependent K\(^+\) channels in the modeled L5 pyramidal cell. e, Relationship between the firing rate in the up-states and the mean membrane potential with Ca\(^{2+}\) and Ca\(^{2+}\)-dependent K\(^+\) currents. The input pairwise correlation strength is 0.1 and the mean input firing rate is 30 Hz.

Here, we take a theoretical approach to study the dynamics of the membrane potential in single neurons given a physiologically constrained representation of the temporal properties of its afferent signals. This model shows that, the correlation properties of the input induce a bi-stable dynamics (up-down states) of the sub-threshold membrane potential. The sub-threshold dynamics of our model shows an increase of the power of the \(\gamma\)-frequency band during up-states, and an increase in the standard deviation and fraction of time spent in the depolarized state qualitatively similar to experimental results from intracellular studies (Anderson et al., 2000). Furthermore, we show that the quantitative match with the experimental data can be improved upon by introducing more detail into the cellular model (i.e. Ca\(^{2+}\) and Ca\(^{2+}\)-dependent K\(^+\) mechanisms). We subsequently introduce a number of indices to quantify the relationship between the dynamics of a cortical network and the intracellular dynamics. In addition, we show that cell morphology is a critical parameter for the induction of up- and down-states in the membrane potential dynamics. Hence, our results show that the statistical analysis of the subthreshold potential of single neurons can provide a direct measure of the dynamics of a cortical circuit.

### 3.2 Materials and Methods

In the following we describe a detailed model of a cortical neuron and a procedure to produce synthetic input spike trains with physiologically realistic first order, i.e. firing rates, and
second order statistical properties, i.e. pairwise correlations. Subsequently our methods of analysis are introduced.

A. The cellular model

A morphologically detailed layer 5 pyramidal cell (Bernander et al., 1994a; Bernander et al., 1994b; Destexhe and Paré, 2000) is simulated using the NEURON simulation environment (Hines and Carnevale, 2001) (Figure 1a). The computer code of the modeled cell can be found in the CD on the back-cover of this thesis. The original anatomical data are kindly made available by J.C. Anderson & K.A.C. Martin. The parameters for the passive properties, HH-like channels in the soma and the synapses (4000 AMPA, 500 GABAa, 500 GABAb) are selected according to the available literature and previous computational studies (Bernander et al., 1994a; Agmon-Snir and Segev, 1993; Bernander et al., 1994b; Mel, 1993; Destexhe and Paré, 2000) as follow: $R_i = 200 \, \Omega \text{cm}$, $C_m = 1 \, \mu F/cm^2$, $T = 36 \, ^\circ C$, $g_{\text{leak}} = 0.065 \, \text{mS/cm}^2$. We deliberately keep the cell as simple as possible to avoid the introduction of strong a priori hypotheses. For the cell as a whole, we tune the parameters to obtain a consistent input-output firing rate transfer function. As a control we use a second cell model with a different morphology (spiny stellate neuron, kindly made available by Y. Banitt and I. Segev) and include active mechanisms ($Ca^{2+}$ dynamics, fast repolarizing $K^+$-currents, $Ca^{2+}$ dependent $K^+$ currents, spike frequency adaptation, and $Na^+$ channels, parameters as in Banitt & Segev, manuscript in preparation). We also check for the robustness of the results presented in respect to changes of the dynamics of AMPA and GABA synapses. These controls confirm the generality of the phenomena as reported below.

B. Input stage, first order statistics

The input stage reproduces measured anatomical and physiological conditions (Douglas and Martin, 1990). Layer 5 neurons in cat’s visual cortex do not receive significant input from LGN; the overwhelming majority of inputs are cortico-cortical afferents (Gabbott et al., 1987). The distributions of orientation preferences of the afferent excitatory signals to our model neuron is graded and matches the experimentally observed specificity of intra-areal cortico-cortical connections (Kisvarday et al., 1997; Salin and Bullier, 1995) : 57% of the inputs originate from neurons with similar ($\pm30^\circ$) orientation preference. 30% and 13% of afferents originate from neurons with a preferred orientation differing by between 30'-60' and
60°-90° respectively from the neuron under consideration. This connectivity automatically provides the cell with a feedforward mechanism for its orientation tuning. Whether or not this mechanism correctly describes the origin of orientation-selective responses in primary visual cortex is still unresolved (Sompolinsky and Shapley, 1997) and not within the scope of the present study. The firing rates of the inputs are determined with a “typical” visual stimulus in mind, i.e. an oriented grating. The maximum input firing rate of the optimally stimulated neurons is set to 85 Hz. Non-optimally stimulated cells are assumed to have an orientation tuning of ±30° half width at half height, and the firing rate is reduced accordingly. In addition, background activity is simulated with uniform, uncorrelated 6 Hz activity. Inhibitory inputs are implemented with a broader orientation tuning than excitatory inputs. We also check for the robustness of the results presented in respect to changes of the tuning properties of the inhibition (variations of the σ of the Gaussian-fit of the tuning curve). No relevant effects on the observed phenomena are found. The input spike trains are generated with the MATLAB software package (MatWorks Inc. Natick, MA).

C. Input stage, second order statistics

The temporal dynamics of the input stage reproduce, in a controlled fashion, the correlation strengths and time lags that have been observed experimentally. In the following the temporal precision of the correlations will be held constant, with the width of the peaks in the cross-correlograms always on the order of 10 ms. Furthermore, the time lags of the correlations are determined by a parameter that is kept fixed in all simulations (König et al., 1995b). We only vary the correlation strength, i.e. the height of the peaks in the cross-correlogram. We will refer to these dynamical features as to the correlation “structure” of the inputs (König et al., 1995a; Roskies et al., 1999) (Figure 1b-c). In our model, the inhibitory inputs follow the same correlation structure as the excitatory inputs. The algorithm used for the generation of pairwise correlations allows us to control the correlation strengths. All simulations are analyzed in epochs of 10 s duration. For the quantitative evaluation of our data we use a five-parameters Gabor fit of the cross-correlograms (König, 1994). We calculate the strength as the area of the peak of the Gabor function divided by the area of the rectangular portion of the graph under the peak, delimited by the offset. This evaluation differs from the more typical “Relative Modulation Amplitude” (RMA), but allows a more robust estimate of the correlation strength. The rational behind the synthetic spike train generation algorithm is that for each pair of spike trains there are intervals in time when the probability of correlated
spiking activity is increased. The method used closely resembles other well-known algorithms to produce correlated spike trains (Stroeve and Gielen, 2001; Feng and Brown, 2000) (the source code is available from the authors upon request). The statistical properties of the synthetic spike trains conform to known physiological constraints, and for this reason we will refer to them as "physiologically realistic inputs". We do not introduce a dependence of the strength of correlation on the orientation tuning of the neurons. This conforms to the hypothesis, that the synchronization pattern induced in the network reflects global stimulus properties and is not a fixed property of the network (Singer and Gray, 1995). In particular, when only a single stimulus is presented, the strength of synchronization of neuronal activity in the primary visual cortex over short distances is found not to depend on the orientation tuning of the neuron (Engel et al., 1990). We do not expect that introducing additional parameters and a dependence of synchronization strength on the orientation tuning would significantly alter the results, as orthogonally tuned neurons provide only a small fraction of the total input due to their low activity and few connections.

D. Higher order correlations

Neuronal interactions in the cortex are measured solely in terms of correlations of the activity of pairs of neurons. Hence, the algorithm used here synthesizes spike trains with a specified pairwise correlation that satisfy those observed in the neuronal interactions in the cortex (Figure 1b,c). Nevertheless, due to the high level of convergence observed in the cortex, higher-order statistical events must and do appear. This holds even for the low values of the experimentally observed pairwise correlations (Destexhe and Paré, 2000; Bothé et al., 2000; Grün et al., 2001). Higher-order events indicate episodes of the presynaptic dynamics characterized by spiking activity from a large fraction of afferent neurons, occurring all together in a small time window of the order of a few milliseconds. How these nearly synchronized events naturally emerge from the pairwise correlations constraint, has been formally investigated (Bothé et al., 2000). It can be intuitively understood considering that the number of pairwise coincidences rises quadratically with the number of afferents, and that the number of spikes available to generate such coincidences rises only linearly with the number of afferents. It follows, that spikes have to be "used" multiple times to generate coincidences, i.e. higher-order correlations must appear. With an increasing number of inputs the effect is amplified. This is important when considering realistic values for the number of afferent inputs to a given cortical cell, typically of the order of $10^4$. At this level of convergence the
statistical effect explained above, becomes dominant and higher order events are a prominent feature of the dynamics (Mazurek and Shadlen, 2002).

E. Analysis of intracellular dynamics

The intracellular dynamics is evaluated using different measures in the time and frequency domain. The up- and down-states of the subthreshold membrane potential are determined as in Anderson et al. (2000) using two thresholds. A sliding window of 50 ms is used to find segments in which the membrane potential is above the up-threshold for more than 60% of the time. We use a similar procedure for identifying the down-states, i.e. the membrane potential is below a down-threshold. For the cumulative probability distribution of the membrane potential any section where the membrane potential exceeds the up-threshold is included in the analysis. To eliminate the spikes and to check for the inverse relationship between the spike threshold and the slope of the rising phase of the action potential we use the same procedure as in Azouz et al. (2000). We compute an a-dimensional index, named “S” that accounts for the dependence of the bimodality on the input correlation strength,

\[ S = \frac{V_{\text{max}} - V_{\text{min}}}{|V_{\text{max}}|} \]

where \( V_{\text{max}} \) and \( V_{\text{min}} \) are the location of the peaks in the membrane potential histograms (Figure 2a,b).

3.3 Results.

A. Emergence of up-down states

When we provide the model neuron with correlated inputs as explained above, the membrane potential at the soma is characterized by up and down-states of the dynamics (Fig. 2a,b left panels). However, when the cell is stimulated with uncorrelated background activity this bistability of the dynamics disappears (Fig. 2c left panel). Indeed, in physiological recordings in primary visual cortex using stimulation paradigms that are not associated with correlation structures, i.e. awake cats during spontaneous activity, up-down states are not observed (Anderson et al., 2000; Steriade et al., 2001)(see Fig. 2c). When comparing the results of the simulation to recently published data (Azouz and Gray, 2003) the similarities are obvious. Compared to other experimental studies, however, a remarkable difference in timescales is apparent (Fig. 2a). In the purely passive model the duration of the up-states is typically
around 30 ms, which is at least a factor 10 lower than the experimental value. As discussed in Wilson and Kawaguchi (1996) the duration of the up-down states are mainly determined by the kinetic properties of \( \text{Ca}^{2+} \) and \( \text{Ca}^{2+} \) dependent \( \text{K}^{+} \) currents. Including these active mechanisms in our model shows that this holds true also in the simulation (Fig. 2d). In comparison to the passive model the duration of up-states increases by a factor 10. It reaches a duration of 300 ms resulting in an improved match to the experimental results.

**B. Quantification of intracellular dynamics**

To analyze the relationship between network and single cell dynamics in a more quantitative way, we compare a number of characteristic measures of the simulated neuron to known physiological results (Anderson et al 2000). First, as reported in the literature we find a strong correlation between the membrane potential in the up-state and the spiking frequency (Fig. 2e and 3a). Second, we find an increase of the standard deviation of the membrane potential in the up-state that matches that observed in the visual cortex (Fig. 3b). Finally, we observe an increase of the power in the 20-50 Hz frequency band in the up-state vs. the down-state (Fig. 3c). These three findings match experimental results that are considered to be the central characteristics of up-down state dynamics (Fig. 3a-c right side). Our results show that these characteristics emerge naturally in a detailed model of a cortical neuron when exposed to realistically structured input.
Figure 3.

Characteristic features of up- and down-states. a, The firing rate in the up-state (vertical axis) is shown as a function of the membrane potential in the up-state (horizontal axis) for both the simulation of a passive model (left) and the experimental data (right). In both cases the average membrane potential in the up-state is correlated with the firing rate of the cell in the up-state. The difference in the scale between the left and right panels depends on the mean input-firing rate chosen for this specific data set. The input correlation strength is 0.1 and the mean firing rate of the input is 85 Hz. See Fig. 2d,e for a comparison of the active model with the experimental data. b, The standard deviation (STD) of the membrane potential of the simulated neuron is increased in the up-state as compared to the down-state (left). The inset shows the subthreshold dynamics during stimulation and spontaneous background activity, respectively. The corresponding experimental data are shown to the right. In both cases stimulation increases the variance of the subthreshold membrane potential. c, The plot of the power spectra in the 20-50 Hz frequency band of the membrane potential for the optimal stimulation...
condition (left panel) shows an increase in the up-state as compared to the down-state. The same phenomenon is visible in the plot of the experimental data (right panel). As no information is available on the normalization used for the power spectra in Anderson et al. (2000) we use arbitrary units and a comparison of the absolute scale in the two panels is not possible. The vertical and horizontal dotted lines indicate the median for each corresponding axis; the light gray circle is the center of gravity of the distribution for a better comparison with the result of the simulation as shown in the left panel. The input pairwise correlation strength is 0.1 in Fig. 3a and 3c, and it is 0.2 in Fig. 3b, while the mean input rate is always 85 Hz.

As a next step, we investigate measures of intracellular dynamics and relate them to the properties of the network’s activity. We define a set of indices to capture different aspects of the subthreshold activity. The first of these quantifies the strength of the correlations in the network activity and the bimodality of the membrane potential histogram (S-index). Increasing the correlation strength from its typically reported value of about 0.1 as used above (König et al., 1995a; Salinas and Sejnowski, 2000; Kock et al., 1995), leads to an enhancement of the bimodality of the membrane potential histogram, resulting in a “sharpening” of the two peaks (Fig. 4a). This index is a monotonically increasing function of the correlation strength (Fig. 4b). The next index represents the fraction of the total Time spent in the Up-State (TUS). For each simulation the total time the membrane potential surpassed the up-threshold is divided by the total simulation time. This index is related to the integral of the peaks in the histograms, as explained in Anderson et al. (2000). The results indicate that this measure is strongly dependent on the input correlation strength: The TUS index is measured to be 7%, 13%, and 42% for the correlation strengths of 0.01, 0.1, and 0.2, respectively. The third measure relates the correlation strength of the inputs and the Cumulative Probability (CUP) distribution of the up-state (Anderson et al., 2000). The cumulative probability distributions of the time intervals during which the membrane potential is above the up-threshold are computed for different values of the input correlation strengths. Though it is not independent from the TUS index, it is a refinement of the previous index in that it controls for possible artifacts due to the spike-cutting procedure (Fig. 4c). The CUP measure can easily separate the diverse input correlation strengths, i.e. 0.01 pairwise correlation strength (black lines) from 0.2 pairwise correlation strength (light-gray lines). Finally, the fourth index measures the Slope At Threshold (SAT) and thus characterizes the relationship between the input correlation structure and the dependence of the voltage threshold for the spike generation on the maximum slope of the rising phase of an action potential (Fig. 4d,e). Indeed, (Azouz and Gray, 2000) have observed an inverse relationship between the maximum slope of the rising phase of an action potential and the voltage
threshold for the generation of the spike (Fig. 4e). A similar inverse relationship also appears in the simulated neuron (Fig. 4d). More importantly, we find that the slope of the fit quantifying the relationship between the maximum slope of the rising phase of an action potential and the voltage threshold for the generation of the spike provides a measure of the input correlation strength (Fig. 4f). This result indicates that this index tends to decrease with increasing correlation strength. These analyses of the membrane potential in the simulation data suggest that the four indices can be used to extract the correlation strength within the network activity from the intracellular dynamics.
Figure 4

Sensitivity of the membrane potential to the input correlation strength. a. Histograms of the distribution of the membrane potential for three different conditions. The input correlation strength is increased from left to right: 0.01, 0.1, 0.2 respectively. Bimodality emerges and the hyperpolarized peak gets further away with
increasing correlation strength. b. The “S” index (see methods), which quantifies the increasing separation of the peaks in the membrane potential histograms, is shown for five choices of correlation strengths. Note that here and below the data points are connected by lines improved visualization. We have no a-priori hypotheses about specific functional relationships. c. The cumulative probability distribution of the time interval the membrane potential dwells above the up-threshold. It is shown for six trials at two levels of correlation strength each. d. For each action potential of the simulated neuron the maximum slope of the rising phase of the potential during the spiking activity and the threshold potential for the spike generation are shown in a raster plot. e. The identical measure used in an experimental study demonstrates an inverse relationship as well. f. The slope of the corresponding linear fit (solid line in Fig. 4d), provides an index that is related to the input correlation strength. g. To perform a reverse correlation analysis for every transition from down- to up-states a time window was centered in the corresponding population-PSTH at the input stage to identify presynaptic events associated to the transition. The plot shows the average population activity in the temporal vicinity of a down-to-up transition.

In a next step we investigate the causal link between presynaptic higher-order correlation events and up-down states. We perform a reverse correlation analysis of the transition from down- to up-states with the population activity. On average the total presynaptic activity around the transition from down- to up-states shows a sharp peak (Fig. 4g). This indicates that the switch of the intracellular dynamics between up- and down-states is induced by short lasting highly correlated input events. This confirms that up-states are induced by presynaptic higher-order events.

C. Cell morphology

An important question is whether the detailed morphology of a neuron contributes to the emergence of up- and down-states and, if so, what the key properties involved are? We manipulate the gross morphological structure of the pyramidal cell in a series of experiments. First, we delete all morphological specificity of the pyramidal neuron by morphing the cell into a spherical, single compartment of equal surface, while keeping the firing rate transfer function unchanged. This reduces the cell to an Integrate and Fire unit with spiking mechanisms. This procedure has been done with and without Ca\(^{2+}\) and Ca\(^{2+}\) dependent K\(^+\) currents. Second, we morph the cell into a 3-compartment model (basal dendritic tree plus soma; proximal-apical dendritic tree and distal-apical dendritic tree, respectively), that preserves dendritic voltage attenuation (Destexhe, 2001). Third, we morph only the basal part into an equivalent compartment while preserving the apical dendritic tree in detail. In all these cases when exposed to the same inputs used in the simulation experiments described above the up-down dynamics disappear (Fig. 5a). Interestingly, when exposing the I&F model to the
same input statistics and using a parameter choice for the Ca$^{2+}$ currents that was eliciting long lasting bi-stability in the L5 pyramidal cell, we do not find any up-down states. Note that this does not imply it is not possible to find a choice of parameters and input statistics such that bistability would emerge. The interesting observation here is that the parameter set which robustly produces bistability in an L5 pyramidal cell does not work for a single geometrical point. However, when we keep the morphology of the basal dendritic tree unchanged and reduce the apical part to a single equivalent compartment, the qualitative aspects of the bimodal intracellular dynamics are preserved (Fig. 5b). Thus, we find that in the passive model an intact basal dendritic tree is the minimal condition necessary for the emergence of up-down states.

Figure 5

Impact of the morphology. a, The histogram of the membrane potential for a single spherical compartment, preserving the original input-output firing rate transfer function, shows a central predominant peak and two small satellite peaks. The more depolarized one is an effect of the spike cutting procedure and the more hyperpolarized one is a result of the after-spike hyperpolarization. b, Histogram of the membrane potential with intact basal morphology and a reduced apical one, substituted by a single cylinder of equivalent surface. c, Histogram of the membrane potential of a spiny stellate cell with active mechanisms included (see text for more details). d, Bimodality in the histogram of the membrane potential of an integrate and fire neuron with modified EPSPs’ rising and decaying time constants, 1 ms and 12 ms respectively.
As a further test of the hypothesis that the cable properties of the basal dendritic tree are essential for the generation of up-down states, we test a model of a spiny stellate cell developed by Banit and Segev (in preparation). From the point of view of the gross morphological structure this spiny stellate cell can be considered as a pyramidal cell without an apical dendrite. It thus resembles the morphological characteristics of the cell used in the latter control. It is as if, instead of an equivalent cylindrical compartment, the apical part would have been “cut off”. Furthermore, this model contains a number of active mechanisms (see methods). As Banit and Segev have used this model for a different purpose we extended it with AMPA and GABA synapses supplying correlated afferent input as described above. In this simulation using an alternative detailed model neuron with several voltage dependent mechanisms the same bimodality appears (Fig. 5c). This demonstrates that the basal dendritic tree is an important morphological compartment for the induction of up-down states.

In order to investigate the role of the basal dendritic tree we separate the effects of the interaction of many EPSPs in the dendrites and the effects of electrotonic propagation on individual EPSPs by developing a neuron model, which retains some aspects of dendritic processing, but radically simplifies others. In the real neuron, as well as in the detailed simulation, when a barrage of EPSPs occurs synchronously in several basal dendrites, these long and thin cables quickly become isopotential compartments, each simultaneously depolarizing the soma. Moreover, the temporal filtering properties of these cables have the net effect of prolonging the effective duration of the EPSPs. Note that this temporal broadening is effective even though the intrinsic dendritic time constant, \( \tau \), is lowered by the arrival of massive excitations, which increases the conductance (Pare et al., 1998). The overall effect is a strong, sustained current to the soma. In case this is the decisive aspect of dendritic dynamics generating up-down states, we should observe similar results by increasing the duration of the EPSPs in an Integrate and Fire model without any detailed morphology, i.e. a point neuron. Of course, we have to keep the total charge flow and the input correlation structure unchanged, i.e. correlation strength of 0.1 and a modification of the rise and decay time constants and peak amplitude of the conductance change, \( g(t) \), to keep the integral constant. Also in this simulation up-down states emerge (Fig. 5d). It should be emphasized that the quantitative “mismatch” in the bimodality between Fig. 5d and Fig. 2b is not surprising since the models used are completely different: a L5 pyramidal cell with detailed morphology and a single geometrical point, I&F neuron. We conclude that for the passive
model higher-order events, which naturally result from weak pairwise correlations in the network, combined with physiologically realistic electrotonic dendritic properties, explain the bimodal distribution of the membrane potential and that active conductances shape its detailed temporal properties.

3.4 Discussion.

Up and down states of the membrane potential have been described in a large number of in vitro intracellular studies and in few in vivo studies as well, e.g. (Steriade et al. 2001). What is the functional meaning of this phenomenon for the awake animal is still an issue hotly debated. Several studies highlighted how the anesthetics used during the recordings might be the “artefact” inducing such bistable dynamics, e.g. (McCormick et al. 1985; Steriade et al. 2001). This interpretation would exclude any functional role associated to the bistable dynamics. Other studies emphasized instead the possible role played by up-down states in working memory tasks during everyday behavioral performances, e.g. (Compte et al. 2003).

Those studies that focused on a presynaptic origin as a trigger for the down-to-up transitions, have suggested that synchronous barrages of excitations may be the major agents involved (Wilson and Kawaguchi, 1996). What kind of mechanism in the cortex could be responsible for their generation is an issue that has not been fully resolved. Here we show that indeed, no additional hypothesis other than the well-described weak pairwise correlations is required to fill this gap. However, we also show that in our model such a pre-synaptic source can only account for the bistability in the membrane potential dynamics of the postsynaptic neuron when it is complemented by signal transduction and generation mechanisms derived from a detailed dendritic morphology and active intra-cellular mechanisms. The differential impact of the morphology of the basal and apical dendrites on the response properties of pyramidal cells has been pointed out in other experimental (Larkum et al., 1999) and theoretical studies (Kording and König, 2001). In them, properties of the inputs play a key role in the interaction of apical and basal dendritic compartments. In another study, it has been shown that the dynamic regulation of the dendritic electrotonic length can give rise to highly specific interactions in a cortical network that can account for the differential processing of a multiple stimuli (Verschure and König, 1999).
A. Simplifications and assumptions

The simulations presented in this study incorporate a number of assumptions and simplifications. Although within the framework of the simulation it is possible to use statistical indices to quantify the relationship between membrane potential dynamics and the statistical structure of the inputs, a full quantitative match between experimental and simulation results is difficult to achieve. To understand the reasons behind these differences (standard deviation, Fig. 3b, slope, Fig. 4d-e), it has to be considered that we investigated detailed compartmental models where many known channels and currents (Wilson and Kawaguchi, 1996) have been omitted. In particular, voltage dependent currents with long time constants are known to play an important role stabilizing and prolonging up-down states (Wilson and Kawaguchi, 1996): once the upward or downward transition has occurred active currents contribute to stabilizing the membrane potential in either a up state or a down state. Their duration is related not only to the input dynamics, but also to the kinetic properties of such active mechanisms, which essentially implement a bistable attractor of the dynamics. Without that, the passive filtering properties of the dendrites would simply be responsible for the emergence of stretched-in-time envelopes of the coherent presynaptic events. Up-down states would be triggered but not maintained for prolonged periods. These considerations have been validated by a ten-fold increase in the duration of the up-states as soon as $\text{Ca}^{2+}$ and $\text{Ca}^{2+}$-dependent $K^+$ currents have been included in the model. In view of this, the temptation to include a much larger number of active mechanisms arises. However, it is quickly obvious, that data needed to specify the precise distribution and strength of each mechanism is not available. Therefore, the number of free parameters of the model, to be fitted by reaching a consistent input-output firing rate and other constraints is dramatically increased, and surpasses the number of constraints available. Thus, given our current limited knowledge on the distribution of such channels, including these in the model presented would not help to clarify the relationship between the properties of the input and the subthreshold dynamics. An interesting alternative to the above scenario can be envisioned. Instead of increasing the complexity of the modeled cell, it is possible to lower the complexity of the real cell. Essentially, an experiment can be designed in which the focus shifts from an investigation of the cellular properties of the recorded neuron as such, to using the neuron as a probe to investigate the correlation structure in the network. The main guidelines of the experiment should be to record intracellularly from a neuron in primary visual cortex while presenting different visual stimuli that will induce different correlation structures. Gratings are known to
induce pairwise correlations, while randomly moving dots lead to weak or no correlations (Usrey and Reid, 1999; Brecht et al., 2001; Gray et al., 1990). Applying blockers of voltage dependent channels and/or hyperpolarizing the neuron strongly affect the membrane conductance and simplify the dynamics within the real neuron. The aim is to reduce as much as possible the impact of active mechanisms so that the real cell becomes simply a passive receiver of the input spike trains and their higher order correlation statistics. Reducing the number of parameters that can vary in a real experiment to the smaller set of controlled parameters employed in the simulation study, allows to further validate the conclusions derived from our model against physiological reality. This makes it possible to infer the correlation strength of the activity in the cortical network from the subthreshold dynamics as quantified by the indices described above. In this sense the simulation study facilitates a new experimental approach, using a neuron under non-physiological conditions as a passive probe to investigate the dynamics of the network.

B. The scope of the model

In our simulations, we do not reconstruct a complete visual system, but approximate the first- and second-order statistical structure of the afferent inputs to a single neuron derived from experimental results. This approximation can be experimentally verified by intracellular recordings in area 17 of an anaesthetized cat using full field gratings as visual stimuli. This setup has been used in a fair number of laboratories to demonstrate the existence of weak pairwise correlations in neuronal activity (Bair, 1999). Such synchronized activity has been observed over a spatial extent of several millimeters, roughly matching the scale of monosynaptic tangential connections in the cortex (Singer, 1993). Therefore, a pyramidal neuron in visual cortex samples mainly activity of a region where neuronal activity is weakly correlated. Furthermore, the pyramidal cell reconstructed and simulated in this study has been recorded from and filled in primary visual cortex. Thus our simulations apply to this widely used experimental paradigm. Moreover, pyramidal cells are the predominant neuronal type in the whole cortex, and weak pairwise correlations have been found in many other cortical areas and species as well (Bair, 1999). Thus, there is no obvious reason why the conclusion of the simulation presented here should not apply much more generally.

An other important question pertaining to our study and the physiological data it relates to is whether the phenomena studied here generalize to the awake behaving animal. The impact of the behavioral state on the cortical dynamics is not fully understood and the
bulk of physiological experiments are performed under anesthesia. EEG data shows marked differences in the neuronal dynamics between different behavioral states (Steriade et al., 2001) and we can expect that the detailed dynamics of neuronal activity are affected. Furthermore, it is known that anesthetics influence the dynamics of up- and down-states during spontaneous activity (Steriade, 2001). However, whether the subthreshold dynamics is influenced by anesthetics when visual stimuli are applied is yet unknown. Furthermore, in the few studies where awake cats are used (Gray and Viana di Prisco, 1997; Siegel et al., 2000), correlated activity on a millisecond timescale has been observed, compatible with the results obtained with the anesthetized preparation. Interestingly, a bimodality in the subthreshold dynamics has been observed in slow wave sleep (Steriade et al., 2001). This raises the question of how the correlation structure of neuronal activity during sleep matches that observed under anesthetics. Hence, whether the assumptions made in the present study, and the data they are based on, generalize to awake or sleeping animals has to be further investigated. The few results available suggest, however, that the relationship reported here between network dynamics and up-down states could be valid for different behavioral states.

Targeting well-defined problems at a specific level allowed major advances in the neurosciences. This also led to an enormous diversification and specialization. In this study a description at one level, the single neuron, is related to properties at another level, the network. As a result, a unified view of two well-known experimental phenomena, up-down states and weak pairwise correlations, emerges: They are two separate expressions of the same underlying dynamical process.
Chapter 4

Dynamical Features of High-Order Correlation Events: Impact on Cortical Cells

In this chapter we study the impact of higher order correlation events (HOCE or unitary events) on the response properties of cortical cells. The main goal is to understand how higher order correlation events might be involved in cortical coding mechanisms. In order to address this issue we simulated the dynamics of a population of 5000 neurons, controlling parametrically both their second order and higher order correlation properties to reflect physiological criteria such as mean firing rate, CV and pairwise correlation. We then used this ensemble dynamics as input stage to morphologically reconstructed cortical cells (layer 5 pyramidal cell, layer 4 spiny stellate cell), and to an integrate and fire neuron. Our results show that changes solely to the higher order correlation properties of the network’s dynamics significantly affect the response properties of a target neuron, both in terms of output rate and spike timing. Moreover, the morphological features and voltage dependent mechanisms of the target neuron considerably modulate the quantitative aspects of these effects. Finally, we show how these results can apply to sparseness, neuronal tuning properties, and attentional effects, according to a novel mechanism of signal processing.
4.1. Introduction

The statistical properties of the inputs to a target neuron have a great impact on its response properties, such as the firing rate, the spike timing variability and reliability {}. These statistical features of the inputs are currently not known. Nevertheless, theoretical and experimental investigations suggest that higher order correlation events might play an important role {}. The term Higher Order Correlation Events-HOCE (or unitary events in the following) is used to define time epochs in the activity of an ensemble of cells, characterized by a conspicuous quasi-synchronous spiking of a large fraction of neurons. To be correctly labeled as unitary events, their frequency and the fraction of cells involved, must occur above the by chance level (Grün et al., 2001; Abeles, 1991). In this study we use a computational approach to show that cortical neurons are extremely sensitive detectors of the higher order correlation properties of their inputs.

To prove this results we implemented a numerical algorithm to generate several groups of spike trains (with 5000 spike trains per group), differing only in terms of HOCE properties, but having identical fixed second order correlation properties; mean firing rate, CV, and pairwise correlation strength (see Appendix 1 for a formal definition of these quantities). These groups of 5000 spike trains were then used in a NEURON simulation (Hines et al., 2000) as input stage to morphologically reconstructed cortical cells (L5-pyramidal, L4-spiny stellate) and an integrate and fire (I&F) cell. Thus we could selectively evaluate the impact of unitary events on the output response properties of the modeled neurons, excluding possible effects due to variations in the second order correlation properties. We performed analyses both in the time and frequency domain, in the supra- as well as in the sub-threshold domain, paying special attention to changes in the output rate and spike timing. We showed how HOCE synergistically interacts with cellular morphologies and voltage dependent mechanisms (the electrotonic properties of the cell) modulating the output response. By focusing on the impact of HOCE on the rate of a target cell, we showed how population and life-time sparseness {} of a group of neurons is affected by changes in the higher order correlation properties of the dynamics. Moreover, we performed simulations to show how higher order correlation events can affect the orientation selectivity of a neuron, by modifying its tuning curve. Finally we discuss how the same phenomena could explain well-known results related to attentional effects.
4.2. Method

Population rasters are a common way to visualize the spiking activity of a large ensemble of cells. In these types of plots each row represents the spiking activity of a cell during a given trial. Thus, summing along each column (time bin), the population PSTH can be derived (Rieke et al., 1997). Regarding the population PSTH, going from a discrete to a continuous representation, counting over the y-axis can be thought of as a function of time, \( f(t) \). In order to study the impact of higher order correlation events on the response properties of cortical neurons, we need to find a way to control the network dynamics using a functional, \( \mathcal{N} \), which maps \( f(t) \) to \( \tilde{f}(t) \), while preserving the integral, \( \int f(t) dt = \int \tilde{f}(t) dt \) (i.e. the mean firing rate), the CV of the single-cell spiking activity, and the pairwise correlation strength, i.e. what in the present study we call the second order correlation properties. Such a functional would allow us to selectively manipulate the higher order correlation properties of the network dynamics, while keeping the second order ones constant. A formal analytical approach to describe the partition of the dynamics in a second order and higher order part for the correlations is given by the so called "\( \chi \)-expansion" (Martignon et al., 1995; Caianiello and Grimson, 1975) of the probability distribution function associated to the possible dynamical states of a network, as described by a collection of binary vectors, i.e. the spike trains. We follow an easier way and adopt a numerical approach to implement the functional \( \mathcal{N} \) to make changes in the higher order statistical properties of the dynamics leaving the second order ones unaffected.

A. Description of the algorithm

Several algorithms are found in the literature to produce different levels of correlated activity between spike trains e.g. (Murthy and Fetz, 1994; Bernander et al. 1994; Feng and Brown 2000; Stoeve and Gielen 2000; Salinas and Sejnowski 2000; Kuhn et al. 2003). The MATLAB code to generate the numerical algorithm used here is included in the CD that can be found in the back cover of the thesis. The algorithm has many similarities with previous ones, though it presents a number of original aspects as well, as described later. It works in the following way: within the overall time window of analysis, \( T \), time epochs are selected, during which the probability of
spiking is increased for all the 5000 cells in the population. Nevertheless, neurons spike only in correspondence to a subset of these epochs, and, for any two given cells, there is always a non-zero overlap between such subsets. The total number of possible overlaps depends, in a combinatorial way, on the size of the subsets, which is a controlled parameter of the simulation. It is the structure of the overlaps that determines the pairwise correlations and the different degrees of temporal alignments of the spikes, i.e. the HOCE properties. The epochs are time intervals centered on specific points in time, whose duration and distribution are controlled parameters of the algorithm. We refer to these points in time as to the “seeds” of the dynamics. The inter-seeds intervals, the separation in time between the seeds (or Inter Unitary Events Intervals, IUEI), and accordingly the numerical value of the seeds, can be drawn from a random number generator with different underlying statistical distributions: Poisson, Exponential or Gamma of any order. This allows the creation of correlations with or without overall oscillatory activity (Gray and Viana di Prisco, 1997; Engel et al., 1990). The duration of the time intervals centered on the seeds (i.e. the epochs) determines the precision of the correlations and it can be changed to affect the overlaps between the epochs within the same spike train too. The frequency of the seeds is itself a free parameter. Spikes are assigned within the epochs accordingly to a distribution whose skewness and integral is parametrically controlled. The skewness controls the shape of the peaks in the cross-correlograms, with the possibility to create very “sharp” or “broad” correlation peaks, without changing the correlation strength itself (RMA, see Appendix 1). Instead, the integral of the distribution controls the correlation strength. The spikes assigned to the epochs are some pre-determined percentage of the total number of spikes for each train (which determine the firing rate). The rest of the spikes are then randomly distributed according to a Poisson-process with constraints related to refractoriness (2 ms in the simulation). This assures that the CV of each spike train ranges around one (Dean, 1981). A key point of the simulation is that the seeds of the dynamics, which are the time-markers for the occurrence of HOCE, also generate the pairwise correlations. This is a known fact (Bothé et al., 2000; Amit and Brunel, 1997b), and quantitatively relates the time properties of the cross-correlograms to the temporal features of the unitary events in the population-PSTH.

Thanks to this numerical algorithm, it is possible to create an arbitrary number of spike trains, with fixed average firing rate, CV and pairwise correlation strength, while changing the frequency, time duration and amplitude of the unitary events in a completely independent way.
Some examples are shown in Fig. 1. This algorithm represents a numerical implementation of the functional $N$ as described above.
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Figure 1: Examples of different dynamics produced by the $x$-functional. (a) Left, raster plot and corresponding population PSTH, for a sub-sample of 100 cells firing at 40 Hz. The crosscorrelograms, normalized for the peak amplitude, are shown in the right panels. (b) Uncorrelated spike trains with non-stationary (increasing) firing rate during the first 200 ms. Note that anyway only stationary cases are considered in the study (c) Oscillatory activity in the gamma frequency band (50 Hz) obtained by using a Poisson PDF for the Inter Unitary Events Intervals, IUEI, see main text. (d) Using instead a gamma function, which “fits in between” an Exponential and a Poisson distribution, and adjusting the PDF associated to the seeds-related spikes (see text), it is possible to produce correlated, non oscillatory activity, with sharp satellite peaks at roughly 10 ms time lags, in the crosscorrelogram. (e) Changing the same set of parameters, “smoother” secondary peaks can be produced, with wider central peaks mimicking strong correlations with “lower” temporal precision.

4.3. Results.

We now generate groups of spike trains with different HOCE properties and identical second order ones. First, we analyze the effects produced by the functional $X$ on the network dynamics itself, and then we study the impact of such changes on the response properties of modeled cortical neurons.

In Fig. 2 we plotted the population PSTHs of the ensemble’s activity for three values of the frequency of the seeds: 84, 133, 153 Hz respectively. Pair wise correlation strength, CV and mean firing rate of the spike trains are fixed ($RMA=0.1, CV=1, f=80$ Hz, see Appendix 1). At first sight, no clear differences emerge between the population PSTHs, but as soon as the corresponding histograms are computed (Fig. 2, right column), a change in the bimodality of the distribution is observed. The higher the frequency of the seeds, the stronger is the histograms’ bimodality. This effect has an easy qualitative explanation: an increased frequency of the seeds is related to an increased number of peaks in the population PSTHs. The amplitude of the peaks decreases, but the fraction of the total number of spikes associated to the seeds increases, thus shifting the relative proportion of spikes assigned randomly vs. those that are associated to the seeds, with the result of skewing the histograms.

Power-spectra analysis of the input population PSTHs, Fig. 3b, reveals an increased power only in the 10-20 Hz band when the frequency of the seeds was increased as above. The effect is significant only for pairwise correlation strengths above 0.1. This result fits the previous qualitative considerations regarding the increased fast variability in the PSTHs associated to an increased frequency of the seeds.
Figure 2: Effects of changes in the frequency of the seeds on the presynaptic dynamics. (a) Left, population PSTH for 300 cells spiking at 85 Hz, with pairwise correlation strength of 0.08 (RMA), CV=1, and 81 Hz for the frequency of the seeds. On the right side, the histogram of the population PSTH is characterized by a sharp primary peak, followed by a much smaller “bump”, and a plateau (the seeds’ frequency, ‘Sd’, is reported in the inset for clarity). (b) Increasing the frequency of the seeds to 133 Hz causes an increase of the secondary peak’s amplitude, which increases even more at 153 Hz, (c). In all three cases the mean firing rate, CV and pairwise correlation strength are kept constant and the observed changes in the shape of the histograms are solely due to the variations in the higher order correlation structure (i.e. an increase of the frequency of the seeds).
A. Passive L5 pyramidal cell.

Next, we investigate the effects of the dynamical variations induced by the functional $N$ on a target cell meant as a receiver of the population’s activity. We used three different modeled cells in the NEURON simulation environment (Hines et al., 2000): (1) a detailed compartmental model of a L5 pyramidal cell, (2) a L4 spiny stellate cell and (3) an Integrate and Fire neuron, (see Fig. 3a for a schematic of the morphologies). We chose these three models because they allow us to test the generality of the results when the cell morphology is considered (L5 pyramidal and L4 spiny stellate vs. a single geometrical point neuron, I&F), as well as making possible confrontations between different common cellular morphologies (L5 pyramidal vs. L4 spiny stellate). The details of the parameters used for the L5 pyramidal cell are described in the Appendix 1. For the first group of simulations, the cell was completely passive with only H&H-like mechanisms in the soma to produce spikes (Appendix 1). A typical trace of an intracellular somatic recording is shown in Fig. 3c (dark gray trace). The variability of the output spike train and its firing rate are consistent with those of the inputs, i.e. the balance of the cell (Salinas and Sejnowski, 2000) has been set so that the cell responds at the same average rate of the input network, with a comparable high CV as well.


After removing the spikes from the voltage traces (Azouz and Gray, 2000), we computed the histogram of the membrane potential ($V_m$). The effect of changing the frequency of the seeds (same values as above) is mainly related to variations in the skewness of the membrane potential histograms (Fig. 3e-g). When the frequency of the seeds increases, the amplitude of the more depolarized peak in the histograms increases in respect to the hyperpolarized one. To quantify this effect we used an a-dimensional index (A1/A2-index) defined as the ratio between the amplitude of the two peaks. As shown in Fig. 3d, it’s a monotonic decreasing function of the frequency of the seeds. The interpretation of the phenomenon is again intuitive. More unitary events imply more peaks in the population-PSTH; this in turn would “force” more often the membrane potential toward depolarized states. Since the area of the peaks is proportional to the time spent in the corresponding “polarized” states, then the A1/A2-index is capturing the shift in the subthreshold dynamic.
Figure 3: (a) Morphologically reconstructed cortical cells as used in the NEURON simulations: layer 5 pyramidal cell from cat area 17, and a layer 4 spiny stellate cell, from the same cortical visual area. (b) Power spectra analysis of the three population PSTHs shown in Fig.2. The difference in power, observed only in the 10-20 Hz frequency range, is evident. (c) Example of spike trains for the different cell types. (d) A/A Index vs. Nr. of Seeds. (e) Firing rate vs. Nr. of Seeds.
band, as shown in this panel, disappears for pairwise correlation strength lower than 0.1 (RMA. Appendix 1). (c) Intracellular recording from the layer 5 pyramidal cell, during optimal stimulation. The cell is responding at 85 Hz (consistently with the maximum input firing rate), with a CV=1. The bottom light gray trace represents the same somatic recording with an additional 6nAmp I-clamp to stop the cell from firing. (d) Varying only the frequency of the seeds, without affecting the second order correlation properties, causes a change in the shape of the Vm histograms, (e-g, for 81 Hz, 133 Hz, and 153 Hz, respectively), which have been computed after removing the spikes from the raw traces (Azouz and Gray, 2000). To quantify this change in shape, we plotted the ratio of the more depolarized peak over the less depolarized one, resulting in a monotonic decreasing function of the frequency of the seeds. (h) In the passive model of the layer 5 pyramidal cell, the output firing rate is an increasing monotonic function of the frequency of the seeds. Second order correlation properties are fixed as explained above.

II. Rates and CV.

When analyzing the supra-threshold responses, we found there is no dependence of the CV of the output Inter-Spike-Intervals (ISIs) on the input frequency of the unitary events. The output CV remains constant around a typical value of 1 (Dean, 1981). On the contrary, the CV of the presynaptic IUEIs strongly affects the CV of the output ISIs. This result is not new and it has been found in electrophysiological recordings as well (Stevens and Zador, 1998). Essentially the time variability of the unitary events in the input network constrains the variability of the spike timings in the output spike train.

Concerning the frequency domain, we analyzed the Vm power spectra in the broad frequency band between 5 to 100 Hz: we could not find any significant effect due to changes in the HOCE dynamics. This measure is not anyway comparable to the measure used above: the variable analyzed here is the membrane potential after removing the spikes, while before it was the time dependence of the population activity computed as the total number of spikes emitted by the ensemble at every simulation time step.

A result found when looking at the output rates, is that they are strongly affected by changes in the HOCE frequency. As shown in Fig. 3h the output rates increase as the frequency of the seeds is increased. This again fits the previous intuitive explanation: when the number of seeds is increased, more unitary events are created in the input dynamics. Their amplitude is diminished, since the population PSTH integral (the mean firing rate) is constant, but they are still “big enough” to elicit spikes on the postsynaptic cell. Thus higher rates of seeds implies higher output firing rates.
III. Impact on timing: conditional Probabilities.

In order to understand the impact of the unitary events on the output spike timings, we computed the conditional probability, \( P(S_p | S_d) \), that, given a unitary event (or a seed, ‘Sd’) in the activity of the input network, a spike, ‘Sp’, is emitted by the target cell. Seeds-triggered correlation analysis can numerically approximate the conditional probability. If a seed occurs at time \( t_s \), we look at the spiking activity at the output stage using a time window centered around \( t_s \) and having a width \( T_w = 3 \times ISI \). The use of a variable duration for \( T_w \) has the advantage that the conditional probability does not depend on the specific firing rate (as emphasized in Sec. 3.3). Results are shown in Fig. 4a-c, left column. For comparison we also computed the average network activity within the same time window when a seed appears, and we refer to this measure as to the input seeds-triggered analysis (ISTA), as opposed to the \( P(S_p | S_d) \), which we’ll refer to as the output seeds-triggered analysis (OSTA). The ISTA is essentially the same correlation analysis of the OSTA, using, instead of the output spike train, the population-PSTH (Fig. 4a-c, right panels). As shown in the Fig. 4, the presence of a unitary event in the population activity triggers spikes on the postsynaptic cell. Often the cell spikes more than once (burst) and this accounts for the double peak that appears at a time-lag of roughly 2 ms from the first one (refractoriness). The width of the ISTA is indeed comparable with the width of the cross-correlograms, as explained before (compare, for example, Fig. 4a, right panel, with Fig. 1e, right panel) (Bothé et al., 2000).

Complementary to the OSTA, we computed the spikes-triggered input analysis, STIA, which is a reverse correlation analysis to reveal the presynaptic events that are time-related to the output spikes. As expected, the result reveals the presence of a higher order correlation event, Fig. 4e. Please note that the non-zero abscissa of the central peaks of the ISTA and OSTA (but not of the STIA) is simply due to the specific way the numeric algorithm has been designed.

To characterize the variability of \( P(S_p | S_d) \) while changing the frequency of the seeds, we introduced for the OSTA a measure of efficacy of the unitary event in eliciting postsynaptic spikes, defined as the area of the peaks over the area of the plot under the peaks (cutting at the level of the baseline-offset).
Figure 4: (a-c) Left column, Output Seeds Triggered Analysis (OSTA). This is a reverse correlation analysis to determine the temporal relationship between unitary events in the input activity, and the output spiking activity. The plot shows the total number of spikes in a time interval centered on the time of occurrence of the seeds, normalized...
by the total number of spikes of the spike train. Each plot refers to a different frequency of the seeds. The right panels show the Input Seeds Triggered Analysis (ISTA), where the same procedure is applied, using, instead of the output spike train, the input activity profile (population PSTH). (d) Efficacy of the seeds in eliciting spikes. This parameter has been derived from the OSTA, as the ratio of the area of the peak(s) (cut at the offset level), over the area of the plot below the peaks (i.e. below the offset level). An additional data point for the frequency of the seeds, at 110 Hz, has been used to better evaluate the efficacy’s profile (e) Spikes Triggered Input Analysis (STIA). This is a reverse correlation analysis, obtained by looking at population PSTH in a time interval centered on the time of occurrence of the output spikes. The result emphasizes the presence of a higher order correlation event (HOCE).

This a-dimensional index can assume values that are greater (or equal) than zero. If zero, i.e. a flat plot, the postsynaptic spiking activity is completely unrelated to the seed timings, while a value much greater than zero implies increasing time dependence between output spikes and seeds. As shown in Fig. 4d, this parameter is a decreasing function of the number of seeds. When the frequency of the seeds in the population activity is increased, their amplitude decreases since the mean population-firing rate is kept constant, thus their efficacy in eliciting spikes on a reading out unit is decreased. Thus, the overall output rate is determined by the balance between two opposite factors: the efficacy of the seeds, which decreases with increased seeds’ rate, and the rate of the seeds itself. In case of “high” (>30 Hz) mean firing rates in the population activity, the latter factor wins, and an increase in the output rate is observed. In Sec. 3.4 we will discuss the opposite situation for low activity rates.

Related to the concept of efficacy, there is the idea saturation for the seeds’ frequency. This is an important (technical) point for all the analyses done in this study. A way to understand this effect, is to consider the limit when \(Nr.\text{Seeds} \to \infty\) (note that anyway the maximum number of seeds can be \(\frac{T}{\Delta_{\text{bin}}}\), i.e. the duration of the time window of analysis over the time resolution, see Appendix 1). In this limit case all the time bins are equivalent: they all represent seeds of the dynamic. For this limit situation, the pairwise correlations are destroyed since the probability of common firing between spike trains has been “diluted” all over the time bins and the spiking activity undergoes a kind of random walk dynamic (data not shown). Accordingly after a maximum frequency of the seeds (250 Hz in the simulation), a “saturation point” is reached such that the pairwise correlation strength cannot be held constant, and it starts to decrease (note that this is not a theoretical limit, but a numerical limit related to the algorithm used). The results shown in Fig. 4 are obtained with a choice of parameters far from the limit case and the strength
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of the pair-wise correlations has been held constant for the three different values of the frequency of the seeds.

B. Estimate of the seeds' number.

Next, we show, that using somatic intracellular recording in the modeled L5 pyramidal cell, it is possible to estimate the number of seeds used to generate the unitary events. We run two simulations with identical input stimuli, but during the second simulation, we hyperpolarized the cell with a 6 nAmp current clamp at the soma to stop the cell from firing. This way the underlying subthreshold variability responsible for the spiking activity can be easily accessed, Fig. 3c, light gray trace. We perform three current clump experiments, changing accordingly the frequency of seeds as done before. The results indicate that the membrane potential is an extremely sensitive measure of the frequency of the higher order correlation events of its input-network. Indeed, for increasing frequency of the seeds, the histograms of the membrane potential during the I-clamp experiments have the same qualitative tendency to skew as shown before for the population-PSTHs, (data not shown). To quantify this effect, for all the three plots we computed the voltage (abscissa) values of the more depolarized peaks in the membrane potential histograms. For each histogram, we set a voltage-threshold defined as the abscissa of the peak value minus a constant factor (1 mV). The assumption is that, since the model is purely passive, all the membrane potential fluctuations crossing this threshold can be related to the occurrence of unitary events, Fig. 5a. We then confronted the estimated number of seeds according to this procedure to the values set a-priori in the algorithm to generate the input trains. The estimates are extremely reliable for all the three frequency values: $83 \pm 5$, $133 \pm 5$, $154 \pm 5$ Hz, given the set values of 81, 133, 153 Hz, respectively. This result validates the idea that the subthreshold membrane potential of a passive cell can keep track of the presynaptic higher order correlation events and suggests that simple I-clamp recordings, shutting down most of the membrane potential non-linearities, and eventually manipulating the cell with blockers to make it “as passive as possible”, might allow good estimates of the frequency of presynaptic unitary events (see more in the Discussion).
C. Active mechanisms and different morphologies.

The analyses performed so far have been done working with a passive model of a L5 pyramidal cell. We now test the model with different cell morphologies and a number of voltage dependent mechanisms.

On a first set of experiments we used a morphologically reconstructed L4-spiny stellate cell, inserting on the dendrites non-inactivating Na\(^+\) channels, high-threshold Ca\(^{2+}\) channels, Ca\(^{2+}\)-dependent K\(^+\) channels, muscarinic K\(^+\) channels (I\(_{m}\)) and transient K\(^+\) channels (I\(_{A}\)) (Mainen and Sejnowski, 1999) (Appendix 1). We run again the simulations using exactly the same input statistics. The results show that the seeds-to-rate transfer function still exhibits the same qualitative behavior as observed for the passive model, i.e. the rate is a monotonic increasing function of the frequency of the seeds, Fig. 5b. We then inserted the previously described voltage dependent mechanisms also in the L5-pyramidal cell, plus an anomalous rectifying current, I\(_{h}\), with a positive gradient for the peak conductance going from layer 4 to apical dendrites in layer 1, as experimentally reported (Berger et al., 2001)(Appendix 1). As shown in Fig. 5b, the transfer function still retained the same qualitative features, having a monotonic increasing behavior. Interestingly, such monotonic behavior dramatically changed into a convex one as soon as we got rid of the morphology, by redirecting the same inputs into an I&F neuron (Appendix 1), Fig. 5b. To further elucidate what causes such a change, we performed a sequence of controls by morphing selectively different dendritic parts into an equivalent single compartment, first for the whole basal morphology, then for the apical one, and finally by morphing the whole cell into a 3-compartments model (Destexhe, 2001). We discovered that an intact morphology of the basal dendrites was a necessary requirement for the emergence of the monotonic behavior. One possible explanation is related to the filtering properties of the basal dendrites: these “thin long cables” become isopotential compartments when targeted by a unitary event. Such a quick potential change occurs in parallel across all the basal dendrites involved, and its duration is “stretched” in time due to the passive cable properties of the dendrites (Koch, 1999). The overall effect is a transient, sustained current injection into the soma. This phenomenon cannot be implemented in a single geometrical point, i.e. an I&F neuron.
Figure 5: (a) The histogram of an intracellular membrane potential recording during 6 nAmp I-clamp is used to estimate the frequency of the seeds in the input dynamics. A threshold is set just before the most depolarized peak, dotted vertical line, and all Vm fluctuations crossing the threshold are interpreted as fingerprints of HOCE. (b) Seeds-to-rate transfer functions for different modeled cells: "spny" refers to the L4 spiny stellate cell, SI&F refers to the I&F neuron with stretched EPSPs (see main text), I&F, to the standard Integrate and Fire model, "pyr" to the L5 pyramidal cell with voltage dependent mechanisms (the passive case is shown in Fig. 3h). (c) Dependence of the output firing rate of the L5 pyramidal cell during sub-optimal stimulation. When the frequency of the seeds increases, the rate decreases. This is the opposite behavior in respect to optimal stimulation, as shown in Fig. 3h. (d) Time evolution of the population sparseness. The light gray trace refers to a 153 Hz frequency of the seeds, while the dark gray one to 81 Hz. (e) Histogram of the sparseness trace referred to the 81 Hz frequency of the seeds, and (f) to the 153 Hz case. (g) Increasing the frequency of the seeds causes an increase in the selectivity of the cell. A standard
tuning curve, dark gray trace, is mapped into a narrower and higher-amplitude curve, broken light gray line, as soon as the frequency of the seeds increases from 81 Hz to 153 Hz, respectively.

We tested the hypothesis that the disappearance of the monotonic behavior was related to an electrotonic transformation operated by the basal dendrites, by prolonging the time duration of the EPSPs, altering their kinetic scheme, while leaving the presynaptic dynamics unchanged, thus mimicking the filtering effect. The response properties of such a modified I&F neuron switched again from a convex to a monotonic-like behavior, Fig. 5b. Note that each seeds-to-rate transfer functions in Fig 5b, spans different rate intervals. This is because, considering that every cell model has different electrotonic properties, we adjusted the passive parameters in order to keep the output rate within the 40 to 100 Hz frequency band, meant here as a “consistent” range of output frequencies in respect to the tuning properties of the inputs, see Appendix 1.

We also repeated the analyses done in Sec. 3.1.3 for the ISTA, OSTA, and STIA, with voltage dependent mechanisms and different morphologies (data not shown). We found the same qualitative results as for the passive model of the L5 pyramidal cell. Active mechanisms and different morphologies produced only quantitative differences, in a very similar way as for the output rates, as shown in Fig. 5b.

These results lead to two important considerations. First, active mechanisms in the neuron modify the quantitative, but not qualitative behavior of the seeds-to-rate transfer function. This means that the sensitivity of the neuron to unitary events in terms of output rate, is quantitatively, but not qualitatively, modulated by the voltage dependent mechanisms of the cell. This is true for voltage dependent mechanisms having both short (few milliseconds) and long lasting (hundreds of milliseconds) time constants. Second, unitary events can sort different effects depending on the morphology of the target cell. Note that these two points are strictly related since active mechanisms also modify the electrotonic properties of the dendrites, thus drastically affecting the effective impact of the morphology.

D. A model’s prediction: impact on sparseness.

Given the above considerations, we can now formulate a model’s prediction. Suppose the dynamics of the input network to a target neuron is characterized by fixed pairwise correlation strength, mean firing rate and frequency of the seeds. Let’s assume that the efficacy of the HOCEs in eliciting postsynaptic spikes is very “low”. This implies that the peaks observed in the
population PSTH induce depolarized states in the postsynaptic membrane potential that can barely reach threshold. Thus the probability of firing, given a presynaptic HOCE, is roughly around 50%.

Let’s assume that this scenario relates to the input network to a target cell that is sub-optimally stimulated, i.e. receiving inputs at low firing rate and spiking at low rate as well. Suppose also that the frequency of the seeds is not in the “saturation” limit (as explained above). This means that it is still possible to increase the frequency of the seeds while keeping the pairwise correlation strength constant. In so doing, the amplitudes of the unitary events will decrease even more, thus failing to elicit postsynaptic spikes. The prediction is that the output firing rate will decrease.

We simulated such an input dynamics to the passive L5 pyramidal cell (see Appendix 1) and, as shown in Fig. 5c, we found the expected decrease in the firing rate. This effect is precisely opposite to that found for an optimally stimulated cell, as described above. The main message is that, when the frequency of the seeds is increased, cells that are optimally stimulated tend to increase their firing rate, while cells that are sub-optimally stimulated behave in the opposite way. This result is solely due to variations along the seeds’ dimension (higher order correlations) in the space of the input dynamic, leaving all the second order correlation properties unchanged.

E. Population Sparseness.

Interestingly, the effect described above has been experimentally observed in studies dealing with sparseness (Vinje and Gallant, 2000; Willmore and Tolhurst, 2001). Electrophysiological recordings have shown that stimulation of the non-classical receptive fields (nCRF) induces decorrelations (not temporal, but angular) in the activity of neurons having different tuning properties (Vinje and Gallant, 2000). The quantitative measure of this effect is related to an increase of the separation angle (a measure of similarity in the orientation tuning properties of different neurons), together with an increase in sparseness, which relates to the way information, processed in the cortical network, is distributed among spikes within and in between spike trains (Vinje and Gallant, 2000). Simplifying, following nCRF stimulation, moderate responses tend to disappear and the proportion of small and large responses increases, thus sparseness increases as well. This is typically quantified via the kurtosis of the response distribution (RD), which
represents a formal definition of the sparseness (Vinje and Gallant, 2000; Willmore and Tolhurst, 2001). The reduction in moderate responses observed in the simulation, is associated to an increase in the frequency of the seeds, thus a possible interpretation of the experimental phenomenon could go along this line: for a given neuronal ensemble, if the stimulation of nCRF would correspond to an increase in the rate of the unitary events, cells strongly responding to a given stimulus would respond even more. The same interpretation should hold for cells poorly responding to a given stimulus whose response would be weakened by nCRF stimulation (increased seed rates).

We further develop these ideas by studying how changes in the dynamics of the unitary events affect depopulation sparseness. It has to be emphasized that the increase in sparseness mentioned before, when talking about nCRF studies, was referred to the so-called lifetime sparseness (or kurtosis), which has been shown to be independent of the population sparseness (Willmore and Tolhurst, 2001). We focus now on the latter one.

We bin every input spike train of the synthetic data presented before, using a 30 ms time window and we interpret the corresponding spiking activity as the response to a “virtual” external stimulation. Then, for every bin, we compute the population sparseness using the standard definition \[ K_p = \frac{1}{N} \sum_{j=1}^{N} \frac{(r_j - \bar{r})^4}{\sigma^4} \] - 3, with \( \bar{r} \) and \( \sigma \) the mean and standard deviation of the responses across the population of \( N \) neurons. Its temporal evolution, with a time step of 30 ms and for two extreme values of the frequency of the seeds, is shown in Fig. 5d. Fluctuations are expected due to the presence of unitary events in the population activity. As shown by the histograms of the two traces, Fig. 5e, f, when the frequency of the seeds is increased, sparseness assumes more negative values. This result is in good agreement with predictions made via theoretical considerations about the effects of correlations on sparseness, for example confronting “orthogonal codes”, such as PCA-codes, with “non orthogonal” ones, such as Gabor codes (Willmore and Tolhurst, 2001).

Here we showed that changes in population sparseness can be explained within the general framework of the dynamics of the HOCE. Standard second order correlation properties could be fixed, and effects on sparseness would anyway be observed, due solely to variations in the higher order correlation properties of the network dynamics.
F. Feature selectivity and attentional effects.

A different aspect of the differential impact of the HOCE dynamics is related to the features selectivity of the cell. The observation that increasing the frequency of the unitary events enhances the firing rate of optimally stimulated cells, while decreases the responses of sub-optimally stimulated neurons, implies that the selectivity (tuning properties) of the neurons is affected.

The following example clarifies this idea: suppose that we performed electrophysiological recordings to determine the orientation tuning properties\(^1\) of a cell embedded in a cortical network whose dynamics is characterized by a given frequency of the HOCE. If we perform again the same experiments, while a change in the dynamics of the HOCE has occurred (let’s say an increase in their rate, for simplicity), the tuning curve of the cell would appear strikingly different. This is because the tuning properties of a neuron (tuning width and peak amplitude) are strongly affected by changes in the response properties of the neighboring cells, having similar orientation preferences as the analyzed cell (Kisvarday et al., 1997; Shapley et al., 2003).

Concerning the peak amplitude of the tuning curve, if the seeds’ frequency is increased, optimally stimulated neurons will raise their firing rate, and the peak amplitude of the measured tuning curve will accordingly increase. Conversely, for sub-optimally stimulated cells, an increase in the frequency of the seeds will cause a decrease in the firing rate, and accordingly a decrease in the rate values observed along the “tails” of the tuning curve.

We used the model data, as derived in Session 4.1.2, to quantify this effect. Starting with a standard orientation tuning curve (Ferster and Miller, 2000), with a peak firing rate at 90°, as in Fig. 5g, we produced a change in the frequency of the seeds. We then computed the effects on the firing rate as done for Fig. 3h and Fig. 5c, for the optimal, and sub-optimal responses, respectively. At 80° of orientation, when the seeds’ frequency increased from 81 to 153 Hz, the firing rate of the modeled neuron increased of the 27% (from 75 to 95 Hz), while at 57° it decreased of the 50% (from 14 to 7 Hz). Assuming a linear relationship to derive the rate changes between these two extreme orientations (the simplest hypothesis), we computed a new tuning curve, Fig. 5g, broken line. The peak amplitude and width are clearly affected, reflecting the increased orientation selectivity of the neuron. Note that a similar qualitative effect would be

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\(^1\) We chose the orientation just for simplicity, but it could be any other feature of the stimuli
obtained if the tuning curve change were derived from a different seeds-to-rate transfer function, as in Fig. 5b

We now speculate on the 27% increase observed for the peak amplitude of the tuning curve. This effect, simply due to a change in the higher order correlation properties of the network’s dynamics, might be at the origin of a very similar effect observed in attentional studies. During electrophysiological recordings in awake behaving animals, the firing rate of cortical neurons dramatically increases when the animal is asked, while maintaining fixation, to pay attention to the stimulus that excites the recorded cells (Roelfsema et al., 1998; Roelfsema et al., 2003). The neuronal mechanisms responsible for this effect are not clear. The tempting hypothesis we want to propose is that, at the level of the cortical dynamics, an effect of attention would be to modulate (increase) the higher order correlation properties of the population’s activity (see more in the Discussion); If this would be the case, then, as shown in our model, an increase in the output firing rate would be expected when attention is paid to stimuli that are within the receptive field of the recorded cells, as experimentally observed (Roelfsema et al., 2003). An important prediction of the model, yet not tested experimentally, is that a reduction in the output rate would be expected when attention is paid to stimuli that are suboptimally stimulating the recorded cells. Or, equivalently, that an increase in the separation angle (see above) should be observed for attentional effects, as seen for nCRF stimulations. It is important to stress again that using conventional electrophysiological methods, no changes could be detected in the dynamics of the network considered: second order correlation properties (mean firing rate, CV, pairwise correlation strength), the only ones reliably detectable with currently available recording techniques, could be constant, while changes would be produced solely in the higher order correlation statistics.

4.4. Discussion.

The main results of this Chapter can be listed in three points:

First, cortical cells are very sensitive to variations only in the higher order correlation properties of the input dynamics. This is true for the output firing rates, as well as for the spike timings, as demonstrated by using the Efficacy-index, which quantifies the conditional probability of getting an output spike given a presynaptic unitary event. The morphological features of the target cells play a key role in this respect. The increasing monotonic behavior
observed for the relationship between the output rate as a function of the rate of presynaptic unitary events in a L5 pyramidal and L4 spiny stellate cell, with or without voltage dependent mechanisms, disappears in the point neuron (I&F neuron, Fig. 5b). The signal transformation properties of the basal dendrites seem to play a crucial role, according to the same filtering mechanisms as described in the previous chapter. Moreover the slope (and intercept) of such transfer functions are strongly affected by the specific biophysical mechanisms inserted. This fact has important implications in terms of coding. Assuming that unitary events represent a dynamical substrate for coding mechanisms based on correlations, then the results of this study show that HOCE can synergistically work with the morphological specificities and voltage dependent mechanisms of the cell to greatly enhance the neuronal sensitivity to higher order correlation features of the input dynamics.

Second, we showed that the tuning properties of target neurons are greatly affected by changes in the HOCE dynamics. We found that increase in the presynaptic rate of unitary events have a “differential” effect on the output rate of a target cell: neurons, which are highly responding to a given set of inputs, respond even more when the frequency of the HOCE is increased, while neurons poorly responding to the same set of inputs, respond even less with an equivalent increase in HOCE’s frequency. The results observed are compatible with electrophysiological experiments dealing, for example, with attentional effects and nCRF stimulation, e.g. (Vinje and Gallant, 2000). The increased tuning selectivity that we found for optimally driven cells is also compatible with studies dealing with attention. Indeed, “attentional spots” within the receptive field of a stimulated neuron have been shown to boost its response and increase its stimulus selectivity, e.g. (Roelfsema et al. 1998)

Third, the changes in the higher order part of the population dynamics as simulated in this study, strongly affect the dynamics of the subthreshold membrane potential, thus suggesting experimental validations of the results presented. Indeed, we showed, in simulated experiments, that statistical analyses of intracellular recordings could be very accurate measurements to detect higher order changes in the network dynamics. A possible technique might involve in-vivo or in-vitro patch clamp recordings, and the analyses done in Sec. 3.2. Using blockers, and/or hyperpolarizing the cell, it would be possible to make the recorded cell as “passive” as possible, thus reducing the impact of non-linear responses related to voltage dependent mechanisms.
Moreover, off-line data analysis might be used to compensate for inevitable non-stationarities, such as DC shifts of the membrane potential.

We investigated the three above issues by using a computer model of a pyramidal cell and a numerical algorithm to generate the inputs. A direct experimental approach would be optimal, though it presents a number of problems and limitations. Experimental studies dealing with correlations, commonly characterize the dynamics of an ensemble of neurons describing its second order statistical properties, i.e. single cells firing rates, ISI variability, and pairwise correlation structure. Instead, when dealing with correlations between large groups of neurons ($10^5$ as an order of magnitude), experimental knowledge is available only at the time scale of 100s of milliseconds thanks, for example, to optical imaging recordings, fMRI, EEG etc. On a faster time scale (<10 msec.), the scale of interest when studying higher order correlation events, no direct experimental knowledge is available. Current measurements can allow the simultaneous multi-electrode recordings of the spiking activity of cortical neurons that do not exceed an order of magnitude of $10^2$ neurons (Hoffman and McNaughton, 2002). The problem can be rephrased saying that we have only indirect experimental hints about the statistical properties of the fast variability in the population dynamics.

On the theoretical/computational side, studies dealing with large-scale neural network simulations have shown that HOCE are a natural emerging property of the network’s dynamics (Amit and Brunel, 1997a; Brunel and Hakim, 1999; Amit and Brunel, 1997b). Other theoretical investigations have shown they can degrade the temporal accuracy of a coding mechanism based on rate (Mazurek and Shadlen, 2002), they have been claimed as necessary to explain the reliability of the spike timing (Mainen and Sejnowski, 1995), and to generate high CVs, as generally observed in cortical spike trains (Salinas and Sejnowski, 2000). The computational importance of HOCE becomes even more clear when considering coding mechanisms based on correlations, such as the theory of the “binding by synchronization” (Von der Malsburg, 1981), or dynamical models of information processing, such as the “synfire chains” (Abeles, 1991).

Without going into the details of each of the above considerations, we stress that another limitation regards the lack of experimental knowledge to understand what mechanisms could cause the simulated changes in the dynamics of the HOCE in a cortical network. This reflects the previous idea that if HOCE are difficult to detect, it is even more difficult to detect changes in
their dynamics. On a positive side, theoretical studies have shown that several different mechanisms, such as, for example, synaptic depression (Loebel and Tsodyks, 2002), neuromodulatory effects (Verschure and Konig, 1999), transmission delays (Horn and Opher, 1999), could all contribute to induce significant changes in the higher order correlation properties of a neuronal network.

The algorithm used in this study to generate dynamical changes uniquely in the high order correlation structure of the input spike trains allowed us to make formal, systematic distinction between second order and higher order correlation properties of the network dynamics. It is based on the idea of increasing the probability of common firing during a number of time epochs. Overlapping, but not coincident, subsets of such time epochs are associated to pairs of cells having correlated spiking activity. The number of overlaps is determined by combinatorial constraints and allows the creation of more or less important high order correlation structures. Even though this method differs in the specific details from other more common ones, the idea is reminiscent of multiple interaction processes (MIP) (Murthy and Fetz, 1994, Kuhn et al. 2003).

This study significantly differs in several aspects from previous ones dealing with this problem. The large majority of simulation studies reported in the literature dealing with correlations, investigated the effects of changes in the pairwise correlation strength of the input network on the response properties of target cells (typically point neurons), having poor controls on how the dynamics of the HOCE (frequency, amplitude, width) was affected (for a review see Bair W. 1999, and Salinas E. & Sejnowski T.J. 2001). Accordingly, the effective causes for the observed results could be due to the changes in the higher order correlation properties, rather than to changes in the pairwise correlation strength. The statistical independence of HOCE from pairwise correlation properties in the network dynamics (Caianiello and Grimson, 1975) makes extremely difficult a correct interpretation of the effects produced by “general” changes in the input correlation structures to a target cell. These two potentially independent sources of variability (pairwise correlations and HOCE) can contribute in parallel with different weights to the neuronal response properties, to an extent that has not yet been quantified.
Appendix 1.

The parameters used in the NEURON simulations are similar to the set of parameters used in a number of other modeling studies (for a review, see Mainen Z.F. and Sejnowski T.J. 1999). The cell morphologies are available thanks to the kind concession of John Anderson, Tom Binzegger, and Kevan Martin. The passive properties for the L5 pyramidal and L4 spiny stellate cell (from cat, area 17) are the same: $C_m=1 \mu F$, $G_m=0.07 \text{ mS/cm}^2$, $E_{rev}=-65 \text{ mV}$, $R_i=90 \Omega \text{ cm}$, $T=37^\circ$ Celsius. Standard H&H mechanisms have been inserted in the soma for generating spikes. We used several voltage dependent mechanisms (the mod files are freely available from the official NEURON website http://www.neuron.yale.edu/neuron/): non-inactivating sodium channels, $I_{na}$, with $E_{rev}=50 \text{ mV}$ and $G=500$ and 10 $\text{ mS/cm}^2$ in the soma and dendrites, respectively. $I_{ls}$, in the apical dendrites, $E_{rev}=115 \text{ mV}$ and $G=5.1 \text{ mS/cm}^2$. $I_k$ in the soma, $E_{rev}=-77 \text{ mV}$ and $G=50 \text{ mS/cm}^2$. Calcium dependent potassium channels, $I_C$, $E_{rev}=-77 \text{ mV}$ and $G=30 \text{ mS/cm}^2$, in the apical dendrites. Dendritic and somatic $I_A$, $E_{rev}=-66 \text{ mV}$ and $G=10 \text{ mS/cm}^2$. Dendritic $I_m$, $E_{rev}=-77 \text{ mV}$ and $G=30 \text{ mS/cm}^2$ and finally, only for the L5 pyramidal cell, we used $I_h$ current, with layer-dependent conductances (Berger et al., 2001): $E_{rev}=-50$, with $G=32, 22, 7, 2.5 \text{ mS/cm}^2$ going from layer 1 to layer 4 respectively. The I&F neuron consists of an RC circuit plus a leakage and H&H mechanisms in the soma to make the cell firing. For the synaptic activations, we used standard alpha synapses for both excitations (AMPA) and inhibitions (GABA). $E_{rev}=0 \text{ mV}$, $\tau_1=0.3 \text{ ms}$, $\tau_2=4 \text{ ms}$ for the AMPA, and $E_{rev}=-70, -95 \text{ mV}$, $\tau_1=4.5, 35 \text{ ms}$, $\tau_2=7, 40 \text{ ms}$ for the GABA-a, b, respectively. We inserted 500 GABA-a and 500 GABA-b synapses distributed randomly in the basal dendrite and initial part of the apical trunk. The associated input spike trains follow the same correlation structure of the 4000 AMPA, which are randomly distributed all over the cell. To quantify the pairwise correlation strengths, we plotted the cross-correlograms of pairs of spike trains, which have been fitted with a Gabor function (König, 1994). The ratio of the main peak amplitude over the baseline level (offset) defines the Relative Modulation Amplitude (RMA), which is the quantitative measure adopted for the pairwise correlation strength (König, 1994). The variability of the spike trains is quantified by the CV, which is defined as the ratio of the standard deviation of the inter-spike-interval (ISI) durations over the mean value. The firing rate tuning curve of the inhibitions is broader than that of the excitations, which is plotted in Fig. 5g. The peak firing for the excitations is around 85 Hz, while it is around
40 Hz for the inhibitions. To simulate optimal and sub-optimal virtual stimulations, we divided the 5000 input spike trains in 36 subgroups of different size, representing the fraction of inputs coming from cells having different tuning properties from the target cell, according to known connectivity data (Kisvarday et al., 1997). Each group was firing according to a standard orientation tuning curve: the largest group of cells at 85 Hz, and the smallest group (orthogonal orientation) at 4 Hz, Fig. 5g. This provided the cell with a purely feedforward mechanisms for the orientation tuning. All the simulations were run with a time precision on 1 ms. and total single trial duration, $T'$, of 10 sec.
Conclusions.

In this thesis we used a theoretical approach to characterize the correlation properties of the input network to a cortical neuron on a fast (millisecond) time scale and analysed the implications of the results in terms of neuronal signal transduction and cortical coding mechanisms.

The study of the temporal features of the cortical dynamics at a millisecond time scale has been developed throughout chapter 1 and 2. We used Design theory and Statistical/Combinatorial arguments to investigate the correlation properties of large groups of neurons. We found that three well-studied physiological constraints about high coefficient of variation (CV) in the single cell spiking activity and sub-, supra-threshold correlations between pairs of cells, enforce the emergence of unitary events in the cortical dynamics. The broad scope of the constraints and the statistical significance of the results allow us to conclude that unitary events are natural and preponderant phenomena of the cortical dynamics.

The use of Design theory to develop our proofs is a new element in theoretical/computation Neuroscience. With this approach, we could identify zero-variability systems that we subsequently matched against physiological constraints. Zero-variability systems (Symmetric Designs) have been especially useful to exemplify how the common and “intuitive” reasoning that pairwise correlations in the spiking activity and high CV are sufficient to guarantee the existence of unitary events, is very misleading. To observe higher order events, the sub-threshold correlations constraint must be taken into account. This third constraint, in combination with the supra-threshold correlations one, allowed us to estimate the maximum and minimum amount of time during which two cells could correlate their subthreshold dynamics, and verify the compatibility of our estimates with physiological measurements. If spikes, among all the cells, are very sparsely distributed in time, it is not possible to find an agreement with experimental results. Temporal correlations are required to match physiological data.

To discharge zero-variability systems (Symmetric Designs) and to identify a lower bound for the order of unitary events, we introduced two new statistical methods: the Random Controller (RC) and the Combinatorial Method (CM). The RC method allowed us to “go around” an extremely difficult problem of classifying Symmetric Designs compatible with the
three physiological constraints. It is actually still not known if it is possible to find a direct (analytical) solution to such a classification problem. The CM method also simplified a lot the task of identifying a lower bound for the order of unitary events. Possible straightforward approaches would have been (1) to find some sort of analytical expression to relate experimentally determined dynamical features of the dynamics (mean firing rate, pairwise correlations, CV, etc...) to quantitative properties of higher order correlation events (amplitudes, frequencies, duration, etc...). (2) To classify all the systems with a lower order of unitary events than the one under study, thus narrowing down a lower limit. The CM provided a simple alternative: it allowed the creation of groups of spike trains with a lower degree of higher order events. The description of just one, in between all the possible systems with a lower level of higher order events, is sufficient to identify a lower bound (but not the limit) for the magnitude of the unitary events. Thus, using the CM and RC methods we could avoid dealing with classification problems or complicated analytical approaches.

At a cellular level, the study of the correlation properties of large ensembles of neurons presented here contributes to the hotly debated issue of whether cortical neurons act as coincidence detectors or temporal integrators (Softky, 1993a). If the flow of signals converging onto cortical neurons is smooth in time, the average level of this input is the only available dynamical variable. In contrast, if cortical neurons act as coincidence detectors higher order correlation events are necessary to explain, for example, the high CV in the spike timing (Stevens and Zador, 1998; Softky and Koch, 1993b), the bistability in the subthreshold dynamics (Wilson and Kawaguchi, 1996; Anderson et al., 2000), and spike timing reliability (Mainen and Sejnowski, 1995). Thus, systems with a non-vanishing variability in the population activity are a necessary, minimum requirement for the neuron to act as a coincident detector.

Understanding the issue of higher order correlations in cortical networks is important also for clarifying the consistency and feasibility of different neuronal coding mechanisms, which in one way or another do make assumptions on the cortical correlation properties. This has been known since when synchronous events (unitary events) first appeared in the literature in 1963 with Griffith (Griffith, 1963), who introduced the concept of convergent-divergent chains and discussed their stability. In theoretical and experimental studies they have been labeled with the term “surges” of activity, “higher order events”, “volleys”,
“barrages” of inputs, “conspicuous coincidences”, “unitary events”, “population spikes”, or “large brief excitatory events” (Bothé et al., 2000; Grün et al., 2001; Stevens and Zador, 1998; Abeles et al., 1993; Abeles, 1991; Amit and Brunel, 1997; Martignon et al., 1995; Loebel and Tsodyks, 2002). When considering widely used rate-based models, the key dynamical variable is the total count of inputs in a given time interval, i.e., the rate. Fast variability in the population activity, however, is a source of code degradation (Mazurek and Shadlen, 2002). Population spikes induce high-amplitude “noise” in the inputs, thus degrading the reliability of its spike count. Moreover, they can elicit spikes by a target cell degrading its information transduction. The optimal working regime for such coding mechanisms would be a total absence of fast variability. In contrast, correlation-based models rely on higher order correlation events, as a key dynamical feature used in information processing, e.g. (Von der Malsburg, 1981) (Abeles, 1991). Neurons, acting in a coincidence detection mode, are supposed to be strongly responsive to such unitary events. These correlation phenomena are a central feature of temporal coding schemes. Thus, by providing general statements on when fast variability is necessarily observed in cortical dynamics, our study elucidates under which dynamical conditions the different coding mechanisms can work consistently and optimally.

In the last two chapters, we studied the issue of signal-transformation operated by cortical neurons. In Chapter 3 we focused on the sub-threshold domain. We showed, in a detailed computational model of a pyramidal neuron, that weak pairwise correlations in its inputs, in combination with the electrotonic properties of its basal dendritic tree, cause up-down states of membrane potential dynamics. The rational is that when a barrage of synchronous inputs targets the cell, the membrane potential is quickly shifted toward a depolarized up-state, where spikes are produced. Active mechanisms can then maintain the polarization state for several hundreds of milliseconds. If the electrotonic properties of the cell do not allow a fast-enough depolarization of the membrane potential, the transition from the down-to-up state will not occur. Moreover, several experimental characterizations of up-down states, such as an increase in gamma power and standard deviation of the membrane potential, can be explained in terms of presynaptic correlation structures. The analyses done have shown that not only a qualitative, but also a quantitative agreement can be established with physiological data on sub-threshold bistability as soon as more biophysical mechanisms are included in our model.
Previous explanations of up-down states have suggested that synchronous barrages of excitations may be involved (Wilson and Kawaguchi, 1996) in the triggering of the down to up transitions of the membrane potential. Though, the mechanism responsible for their generation is an issue that has not been fully resolved. Here we show that a cortical dynamics constrained by weak pairwise correlations (sub- and supra-threshold) and high CV could fill this gap by mean of unitary events.

However, we have also shown that in our model such a pre-synaptic source can only account for the bistability in the membrane potential dynamics of the postsynaptic neuron when it is complemented by signal transduction and generation mechanisms derived from a detailed dendritic morphology and active intra-cellular mechanisms. The differential impact of the morphology of the basal and apical dendrites on the response properties of pyramidal cells has been pointed out in other experimental (Larkum et al., 1999) and theoretical studies (Kording and Konig, 2001). In them, properties of the inputs play a key role in the interaction of apical and basal dendritic compartments. In another study, it has been shown that the dynamic regulation of the dendritic electrotonic length can give rise to highly specific interactions in a cortical network that can account for the differential processing of a multiple stimuli (Verschure and Konig, 1999). Thus, our findings indicate that the signal transduction and integrative properties of the basal dendrites might play a crucial role for the emergence of up-down states of the membrane potential.

Up-Down states of the membrane potential can be functionally interpreted as a form of high-rate working memory states (Compte et al., 2003b). Working memory states are typically associated to a persistent activation of neural circuits, maintained through recurrent activity and intrinsic neuronal mechanisms, which represents a “mnemonic trace” of an internal or external stimulus (Compte et al., 2003a). High-rate refers not only to the idea of a neuronal circuit whose neurons have “high” output firing rates, but also to fast transitions between activated and de-activated states in the circuit dynamics. These High-rate states have been hypothesized (Compte et al., 2003b), but not yet experimentally observed, and they are supposed to be the neuronal substrate for very dynamic “memory buffers” used during common behavioral activities. Following these considerations, an up-state can be considered as a memory state, during which the cell “remembers” an excitatory process by keeping its membrane potential depolarized. Accordingly to standard neural network computation, e.g.
(Amit, 1992), the remembering activity, signaled at the circuit level by persistent polarization states, can be associated to the activation (and maintenance) of dynamical attractors described in the multi-dimensional space of the dynamics (Amit, 1992; Hertz et al., 1990; Domany et al., 1994). Thus, the suggested link highlighted by our results would bridge dynamical phenomena traditionally associated to correlations (e.g. synfire chains (Abeles, 1991)) and binding by synchrony (Von der Malsburg, 1981)) with phenomena related to high-rate working memory states (Compte et al., 2003b).

Working memory states are considered a network phenomenon and since we did not implement explicitly a connected network of cells, we could not check for the emergence of such attractor dynamics and its stability properties (for example, feeding back the output onto the input stage). On the positive side several theoretical investigations gave a positive answer to the stability problem, e.g. (Amit and Brunel, 1997), thus suggesting that the ensemble dynamics will not die out or diverge to an epileptic state (Compte et al., 2003b).

The link proposed above between network and single-cell level provides a possible background for experimental detection of higher order structures in neuronal networks dynamics. By introducing several new statistical indices we demonstrated a way to derive the correlation strength of the inputs – and thus in the activity of the network – from the subthreshold dynamics of a single neuron. In this sense, correlated activity in the network and the bimodality of the membrane potential are different views on one and the same phenomenon. An experiment can be designed in which the focus shifts from an investigation of the cellular properties of the recorded neuron as such, to using the neuron as a probe to investigate the correlation structure in the network. Reducing the number of parameters that can vary in a real experiment to the smaller set of controlled parameters employed in the simulation study, allows to further validate the conclusions derived from our model against physiological reality. This makes it possible to infer the correlation strength of the activity in the cortical network from the subthreshold dynamics as quantified by the indices described in Chapter 3. In this sense the simulation study facilitates a new experimental approach based on intracellular recordings, using a neuron under non-physiological conditions as a passive probe to investigate the correlation properties of the network.
In the last part of the thesis we further investigated the signal transformation properties of cortical neurons. We studied how higher order events in the pre-synaptic network to a cortical neuron can affect the response properties of the cell in the supra-threshold domain. Indeed, Chapter 4 is dedicated to the analyses of the impact of unitary events on the output firing rate and spike timing of a target neuron. The results show that unitary events, acting synergistically with cellular morphology and biophysical mechanisms, can significantly affect the supra-threshold responses of cortical neurons.

To investigate the impact of unitary events on the output rate and spike timing of cortical neurons, we paid special attention in systematically separating second order and higher order correlation properties of the network dynamics. The large majority of simulation studies reported in the literature over the last decade, dealing with correlations between the spiking activities of cortical neurons, investigated the effects of changes in the pairwise correlation strength of the input network on the response properties of target cells (typically point neurons), having poor controls on how the dynamics of the unitary events (frequency, amplitude, width) was affected (for a review see Bair W. 1999, and Salinas E. & Sejnowski T.J. 2001). Accordingly, the effective causes for the observed results could be due to the changes in the higher order correlation properties, rather than to changes in the pairwise correlation strength. The potential statistical independence of HOCE from pairwise correlation properties in the network dynamics (Caianiello and Grimson, 1975) makes a correct interpretation of the effects produced by “general” changes in the input correlation structures to a target cell extremely difficult. These two (potentially) independent sources of variability (pairwise correlations and higher order correlation events) can contribute in parallel with different weights to the neuronal response properties, to an extent that has not yet been quantified, thus making extremely difficult any interpretation of the results.

Using an algorithm that allowed us to generate selective changes solely in the higher order correlation structures (HOCE-frequency) of the inputs, we found that the output firing rate of a target neuron is significantly affected by such changes. Moreover, also the probability of firing, following a presynaptic unitary event, significantly depends on the frequency of unitary events, given that the lower order correlation properties are fixed. These results indicate that cortical neurons are very sensitive to selective changes in the higher order structures in their inputs.
The importance of the morphological and biophysical features of the target cells has been studied by using different morphologies and voltage dependent mechanisms. The increasing monotonic behavior of the function relating the frequency of the unitary events to the output rate of a L5 pyramidal and L4 spiny stellate cell, with or without voltage dependent mechanisms, disappears in the I&F neuron, Fig. 5b in Chapter 4. Moreover the slope (and intercept) of such transfer function is strongly affected by the specific biophysical mechanisms inserted. These results shows that selective changes produced solely in the higher order correlation structure of the network can interact synergistically with the biophysical and morphological properties of a neuron to significantly modulate its sensitivity to such correlated dynamics.

The impact of selective changes, made solely in the higher order structures of the network dynamics, on the output rate of a target neuron has important implications for neuronal tuning properties. We found an interesting “differential” effect, such that neurons, which are highly responding to a given set of inputs, respond even more when the frequency of the unitary events is increased, while neurons poorly responding to the same set of inputs, respond even less with an equivalent increase in unitary events’ frequency. We quantified this effect as an increased separation angle, e.g. (Vinje and Gallant, 2000), for neurons in the ensemble analyzed. Interestingly, similar effects in separation angles have been observed in electrophysiological studies dealing with non-classical receptive field (nCRF) stimulations, e.g. (Vinje and Gallant, 2000). Moreover, considering that the tuning properties of cortical neurons are largely related to the response selectivity of their inputs, e.g. (Ferster and Miller, 2000), we observed, and quantified, a narrowing in the orientation tuning properties of a target neuron following increased frequency of the unitary events. Finally, considering only one of the two differential effects, i.e. the increase in rate for cells optimally responding to a given set of stimuli, we made a “provocative” connection with attentional studies. In view of our results, the increase in firing rate observed in cells whose receptive field is within the attentional spot (Vidyasagar, 1998), could be explained hypothesizing a change in the higher order structure of the network dynamics. Such a change should be an increase in the frequency of unitary events and it could not be detected by standard electrophysiological measurements, which can capture only the second order features of the population dynamics (see Introduction). All together, these results suggest that unitary events in the cortical dynamics could provide a unifying framework to bind together extremely diverse experimental phenomena, ranging from the up-down states to attentional effects.
It would be extremely desirable to test and validate the ideas presented above with appropriate experiments. A possible solution in this sense could come from the observation that changes in the higher order part of the population dynamics as simulated in this study, strongly affect the dynamics of the subthreshold membrane potential. Indeed, we showed in Chapter 4 with simulated experiments, that statistical analyses of intracellular recordings could be very accurate measurements to detect higher order changes in the network dynamics. A possible technique might be to perform in-vivo or in-vitro patch clamp recordings, and repeat the analyses done in Chapter 4 to detect changes in the frequency of higher order correlation events. By using blockers, and/or hyperpolarizing the cell, it would be possible to make the recorded cell as "passive" as possible, thus reducing the impact of non-linear responses related to voltage dependent mechanisms and increasing the match with the simulated experiments. Off-line data analysis might also be required to compensate for other inevitable non-stationarities, such as DC shifts of the membrane potential. Thus the use of specific intracellular recordings supported by the suggested data analyses could provide a way to experimentally detect changes in the frequency of the unitary events.

Following the well-accepted idea that spike-rates and spike-timings are the most relevant coding variables (whatever the coding mechanism is), we showed that they are both significantly affected by dynamical changes of the unitary events. This observation suggests that the results presented so far have important implications in terms of coding. Indeed, the quantitative aspects of the results suggest that unitary events cannot be considered as small "perturbations" that can be average out by the ensemble's activity, but must be considered a dynamical phenomenon, strongly interacting with the "classical" coding variables. Taking the point of view of a cortical neuron, unitary events represent a significant source of intracortical excitation. Their appearance at the input stage of a target neuron is a dynamical event associated with a great increased probability of eliciting output spikes, in a time-related fashion to the occurrence of the presynaptic unitary event. Given that neuronal spikes are commonly considered the "elementary units" of information processing in the cortex, than unitary events have to be incorporated into the coding mechanism.

Note that to finally reach the above conclusion about the relevance of unitary events in terms of coding, we did not follow a straightforward logic presenting a new computational model based on higher order correlations. Instead, we followed again a logic reasoning "by
exclusion”, as discussed above for the first two chapters. By describing the impact of unitary events on classical coding variables, we excluded the possibility that unitary events can not play a role in computation (unless a new form of neuronal computation is proposed, which does not depend on classical coding variables).

In conclusion, all the results presented suggest that unitary events are a dynamical phenomenon associated to a form of neuronal computation based on correlations. Nevertheless the fundamental question remains: “What is this form of computation?” We want to add a short consideration to this discussion emphasizing that unitary events could be compatible with canonical (attractor) neural network computation (Amit, 1992). In this view, unitary events are pulsed, very fast, dynamical events that can transiently cover trajectories in basins of attraction associated to the network dynamics (Amit, 1992). As suggested in recent studies about Liquid State Machines (LSM) (Maass et al., 2002), behavioural tasks, such as for example, object detection and discrimination, do not require the full attractor dynamics. Indeed, the concept of equivalent classes (Maass et al., 2002) has been introduced to indicate fast spiking events associated to dynamical trajectories “close enough” to each other to elicit the same (stable) network output. Computation with unitary events, in the space of the dynamics of standard attractor neural networks, could be associated to the activation of trajectories in a landscape characterized by dynamical attractors. The belonging of a trajectory to a give basin of attraction (without “waiting” for the whole temporal evolution, until the limit orbit or the attractor point is reached) would be enough to perform fast (millisecond) computation, according to the above-mentioned idea of equivalent classes. Unitary events fit nicely in this scenario, reconciling traditional, well-accepted views about computation with (attractor) neural networks and pulsed (synchronous) form of information processing. Interpreted as packages of information travelling through cortical circuits, their dynamical properties (amplitude, frequency, width, slope, skewness, etc...) could convey, in a compact (in time) and robust way (in respect to intrinsic cellular noise or network noise), information about internal or external stimuli, exactly in the same way as spike-rate is supposed to encode properties about sensory stimuli in traditional views of neural network information processing. All these speculations and ideas are based on the possibility, provided by unitary events, to create a framework to harmonize traditional views about neuronal network computation and higher order correlation events in the cortical dynamics.
**Glossary**

**A1/A2 Index:** Measure of change in skewness observed in Vm histograms, following a change in the frequency of Unitary Events.

**Activity Profile:** Plot of the temporal dynamics of the total number of spikes per each time bin, produced by a group of neurons.

**AMPA Synapse:** Glutamatergic (excitatory) synapse

**Balance Incomplete Block Designs:** Type of Symmetric Design.

**Basal Morphology:** Morphology of the basal dendrites.

**Chi-Functional (χ-Functional):** Functional used to modify solely the higher order correlation properties of the neuronal activity, without affecting the second order correlation properties.

**Coefficient of Variation (CV):** Measure of the spike timing variability in single spike trains

**Combinatorial Method (CM):** Statistical method to generate groups of spike trains with a degree of higher order correlations lower than in the cortical dynamics.

**Combinatorics:** Mathematical science that studies the combinatorial properties of ensembles of objects defined and constrained by a set of properties.

**Convergent-Divergent Chains:** Neural Network-like structure made of layers of neurons receiving and projecting to other layers of neurons, according to given degrees of convergence and divergence (from the input to the output layers, respectively).

**Cross-correlograms:** Plot of the (discrete) cross-correlation function computed for pairs of neurons, as a function of the time lags.

**CUP Index:** Cumulative Probability Distribution Function Index.

**Cyclic Difference Sets:** Type of Symmetric Designs.
Design Theory: Field of Combinatorics aiming at characterizing the statistical and combinatorial properties of groups of objects defined (and constrained) by given sets of properties.

Dynamical Constraints (C1, C2, and C3): Physiological data about single cell and pair of cells dynamics, used to constrain the overall population dynamics.

EPSPs: Excitatory Post Synaptic Potentials.

Fano Plane: Simple type of symmetric design.

First Order Statistics: Statistical properties of an ensemble of spike trains that quantify the mean firing rate and the CV of the trains.

GABA Synapse: Inhibitory synapses.

Gabor Fit: Fit with a Gabor function used to quantify the properties of the cross-correlograms.

Gamma Power: Power observed in the 20-50 Hz frequency band.

Graph: (In the context of this thesis) Graphical representation used to derive the matrix-like structure of a Symmetric Design.

Higher Order Correlation Events (HOCE): Correlation properties of an ensemble of neurons higher than the pairwise correlation properties (unless differently specified, as in Chapter 1).

I-Clamp: Current clamp.

I&F Neuron: Integrate and Fire neuron, i.e. a circuitual representation of a neuron reduced to a simple RC circuit (with or without additional leak conductance).

Incidence Matrix: (In this context) Matrix-like representation of a Symmetric Design.

Inter-Spike-Interval (ISI): Time interval between two consecutive spikes.

Input Seeds Triggered Analysis (ISTA): Reverse correlation analysis that highlights the presynaptic activity temporally related to the occurrence of a seed (or UE) in the input dynamics.

Inter-Unitary-Events-Interval (IUEI): Time interval between two consecutive seeds.
Lower Bound Condition: Group of spike trains generated according to the Combinatorial Method.

Liquid State Machine (LSM): Type of recurrent neural network.

Non-Classical Receptive Field (nCRF): (When referred to vision) part of the visual space, outside the classical Receptive Field, where a stimulus can still influence the response properties of a neuron.

Output Seeds Triggered Analysis (OSTA): Reverse correlation analysis that highlights the postsynaptic spiking activity temporally related to the occurrence of a seed (or UE) in the input dynamics.

Pairwise Correlations: Correlation properties between pairs of neurons.

PCA-Codes: Coding mechanism based on Principal Component Analysis.

Peri-Stimulus Time Histogram (PSTH): Plot of the temporal dynamics of the spiking activity of a neuron, computed as a sum of spike trains derived from multiple repetitions of the same stimulation protocol.

Poisson Background (PB): Reference level of activity to quantify the degree of high-order correlation events, obtained by using a group of uncorrelated spike trains having the same first order correlation properties of a CM set of neurons.

Population PSTH: PSTH obtained by summing spike trains belonging to different cells, acquired during the same trial (as opposed to standard PSTH, obtained by summing spike trains belonging to the same cell, acquired during different trials, see above).

Population Spikes: Short (few ms) time epochs during which a large fraction of neurons synchronize their spiking activity.

Random Controller (RC): Statistical method to generate zero-variability systems compatible with C1 and C2 constraints.

Raster Plot: Matrix-like representation of the spiking activity of several neurons (every row is a spike train), acquired during the same trial, or of the same neuron during different trials.

Relative Modulation Amplitude (RMA): Quantitative measure of the pairwise correlation strength, obtained as the ratio between the peak amplitude of
the main peak of a Gabor fit of a cross-correlogram over the offset parameter of the same fit.

**Response Distribution (RD):** Frequency histogram of the response (rate) amplitudes of a population of neurons.

**S Index:** Separation index, quantifying the distance between the up and down peaks appearing in Vm histograms in bistable cells.

**SAT Index:** Slope At Threshold index. It quantifies how the differential sensitivity of the spike-generation mechanism to the time derivative of the membrane potential is affected by changes in the frequency of Unitary Events.

**Seeds:** Time points (used by the numerical algorithm described in Chapter 4) with increased probability of spike generation. They represent the time-marks for the formation of unitary events.

**Separation Angle:** Index used to quantify the degree of similarity between the tuning properties of cortical neurons.

**Sparseness:** Kurtosis of the response distribution function.

**Spike-Triggered Input Analysis (STIA):** Reverse correlation analysis that highlights the presynaptic spiking activity temporally related to the occurrence of a spike in the output activity of a neuron.

**Symmetric Designs:** (in this context) Group of objects whose reciprocal properties are determined by a given set of combinatorial constraints, and whose overall population-PSTH has a zero degree of variability.

**Synfire Chains:** Groups of functionally connected neurons, representing the neuronal substrate for the generation and propagation of highly synchronous spiking activity in the cortex.

**TUS Index:** Time in the Up-State index. Fraction of the total time during which a bistable cell is in an up-state.

**Unitary Events:** Dynamical phenomenon, occurring in brief time epochs, during which a large fraction of cells spike in a synchronous fashion. The statistical significance of such phenomenon must be much above the by-
chance level, computed according to the underlying statistical processes that generate the spiking dynamics.

**Up-Down States:** Polarized (depolarized and hyperpolarized, respectively) states of the membrane potential.

**Zero Variability Systems (ZVS):** Group of spike trains whose activity profile has no variability (of any degree) in the millisecond time scale. Here, it is used as a synonymous of flat population-PSTHs.
### Notations and Symbols

<table>
<thead>
<tr>
<th>Notation</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>Ca</td>
<td>Calcium currents</td>
</tr>
<tr>
<td>Cm</td>
<td>Membrane Conductance</td>
</tr>
<tr>
<td>Cs</td>
<td>Correlation strength</td>
</tr>
<tr>
<td>$\Delta t_{bin}$</td>
<td>Duration of the smallest time bin in a spike train</td>
</tr>
<tr>
<td>$\Delta t_{dec}$</td>
<td>Time interval during which the Vm of two cells are not correlated</td>
</tr>
<tr>
<td>$\Delta t_{corr}$</td>
<td>Time interval during which the Vm of two cells are correlated</td>
</tr>
<tr>
<td>$E_{rev}$</td>
<td>Reversal potential</td>
</tr>
<tr>
<td>f</td>
<td>Mean firing rate</td>
</tr>
<tr>
<td>$f_{pr}$</td>
<td>Frequency of spike insertions by the Random Controller</td>
</tr>
<tr>
<td>$g_x$</td>
<td>Membrane conductance for x-mechanism</td>
</tr>
<tr>
<td>G</td>
<td>Membrane conductance per $\mu$m$^2$</td>
</tr>
<tr>
<td>$I_x$</td>
<td>Ionic current through the x-channel</td>
</tr>
<tr>
<td>K</td>
<td>Potassium ions</td>
</tr>
<tr>
<td>$K_p$</td>
<td>Population sparseness</td>
</tr>
<tr>
<td>Lx</td>
<td>Cortical Layer (typically Layer 5)</td>
</tr>
<tr>
<td>n</td>
<td>Number of spikes per time bin inserted by the Random Controller</td>
</tr>
<tr>
<td>$n_s$</td>
<td>Number of spikes per train in the Combinatorial Method</td>
</tr>
<tr>
<td>$n_o$</td>
<td>Number of spikes intersections for the Combinatorial Method</td>
</tr>
<tr>
<td>N</td>
<td>Total number of spikes produced by the population in a time T</td>
</tr>
<tr>
<td>$N_a$</td>
<td>Sodium ions</td>
</tr>
<tr>
<td>$N_{bin}$</td>
<td>Total number of time bins, of duration $\Delta t_{bin}$, in the time window T</td>
</tr>
<tr>
<td>$N_{in}$</td>
<td>Total number of neurons in the population</td>
</tr>
<tr>
<td>$P_r$</td>
<td>Probability</td>
</tr>
<tr>
<td>$P'_{x,y}$</td>
<td>Block of order ‘r’ with ‘x’ spikes per spike-train and ‘y’ intersections of ‘1’s per each pair of spike-trains.</td>
</tr>
<tr>
<td>$P(x</td>
<td>y)$</td>
</tr>
<tr>
<td>r</td>
<td>Order of the blocks (degree of HOCE in a block)</td>
</tr>
<tr>
<td>$R_a$</td>
<td>Axial resistance</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>$S'_{x,y}$</td>
<td>Sub-block of order ‘r’ with ‘x’ spikes per spike-train and ‘y’ intersections of ‘1’ s per each pair of spike-trains.</td>
</tr>
<tr>
<td>$Sp$</td>
<td>Spikes</td>
</tr>
<tr>
<td>$Sd$</td>
<td>Seeds</td>
</tr>
<tr>
<td>$T_1$</td>
<td>Average time of co-selection of a given neuronal pair by the RC</td>
</tr>
<tr>
<td>$T_2$</td>
<td>Average time between two correlated spikes in a neuronal pair according to the parameter Cs</td>
</tr>
<tr>
<td>$T_f$</td>
<td>Free-time parameter</td>
</tr>
<tr>
<td>$T_u$</td>
<td>Used-time parameter</td>
</tr>
<tr>
<td>$T$</td>
<td>Total duration time of a spike train</td>
</tr>
<tr>
<td>$V_m$</td>
<td>Membrane potential</td>
</tr>
<tr>
<td>$V_{\text{max}}$</td>
<td>Voltage value of the more depolarized peak in $V_m$ histograms</td>
</tr>
<tr>
<td>$V_{\text{min}}$</td>
<td>Voltage value of the more hyperpolarized peak in $V_m$ histograms</td>
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Reference List


Amit, D.J. and Brunel, N. Dynamics of a recurrent network of spiking neurons before and following learning. Network 8:3731997a.


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Lewis, B.L. and O'Donnell, P. Ventral tegmental Area Afferents to the Prefrontal Cortex Maintain Membrane Potential "Up" States in Pyramidal Neurons via D1 Dopamine Receptors. *Cerebral Cortex* 10:1198-1175, 2000.


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