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High-order events in cortical networks: A lower bound

Andrea Benucci,[1,*] Paul F. M. J. Verschure,[2] and Peter König[2]
[1]*Smith-Kettlewell Eye Research Institute, 2318 Fillmore Street, San Francisco, California 95115, USA*
[2]*Institute of Neuroinformatics University & ETH Zürich, Winterthurer Strasse 190, 8057 Zürich, Switzerland*

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It is commonly believed that information processing in cortical networks involves the collective spiking activity of neuronal assemblies. Nevertheless, due to current technical limitations in multielectrodes recording methods, it is not possible to tackle this issue with direct experimental measurements. In this study we simulate spiking activity of large ensembles of cells focusing on the temporal correlation properties of the neuronal dynamics, and demonstrate that transient, fast synchronization of large groups of cells is a natural phenomenon of the cortical activity. To prove this result we use a statistical approach (based on combinatorics), and knowledge derived from a previous research work [A. Benucci *et al.*, Phys. Rev. E **68**, 041905 (2003)]. We quantify the degree of synchronous activity by computing a lower bound for the fraction of cells participating in fast (few milliseconds) synchronous events. Finally we discuss the implications of the results found in terms of cortical coding mechanisms.

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I. INTRODUCTION

Neurons in the cortex, when excited by neighboring cells by virtue of external stimulation or spontaneous intracortical activity, produce action potential (spikes). How the activity of billions of cells translates into different types of computation and information processing is still unknown. A primary limitation for the understanding of this problem is the technical impossibility of recording spiking activity from thousands of cells at the same time. Nevertheless, there is a growing consensus that the collective activation of large pools of neurons does play an important role, e.g., Refs. [1–4].

In a previous study [1], overcoming these experimental limitations, we used a theoretical approach to prove that the collective spiking activity of large ensembles of neurons cannot show variability only in the hundreds of milliseconds time scale (as shown by electroencephalography and functional magnetic resonance imaging studies) but must be characterized by "some degree" of fast variability at the millisecond time scale, i.e., the temporal scale where experimental methods cannot be of help. In Benucci *et al.* [1], we reached qualitative results, thus we did not discuss in a quantitative way the statistical significance of the findings.

In this new study we want to quantify the magnitude of such fast variability. We will demonstrate, using again a theoretical approach, that, under very general dynamical conditions, the spiking activity of large pools of neurons is characterized by brief epochs of highly synchronized activity (unitary events or high order correlation events hereafter) and we will quantify the significance of the results by computing a lower bound for the amplitude of cortical unitary events. In the Discussion we will consider the implications of the findings in terms of neuronal coding mechanisms.

II. METHOD

The mathematical tools we will use to derive theorems and proofs are based on standard statistical and combinatorial analysis. We implement one model, called the combinatorial method in the following, to generate simulated spiking dynamics of large ensembles of neurons characterized by a degree of high order correlations lower, by construction, than the cortical one. We then quantify the statistical significance of unitary events in the modeled dynamics and show that unitary events are a preponderant dynamical phenomenon. Given that the combinatorial method has been designed to underestimate the degree of cortical high order correlation events, we will finally conclude that unitary events are significant phenomena of the neuronal dynamics as well.

To show that the chosen model underestimates the degree of cortical high order correlation events, we will use knowledge about three physiological "constraints," as introduced in the previous paper [1]. They are well-known 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 interspike intervals over their mean, i.e., the coefficient of variation (CV) assumes values close to 1, suggesting that the spike timing statistics can be described in terms of a Poisson process [5]. C2: Pairs of cells sharing similar orientation properties tend to synchronize their activity [6]. 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 [7,8]. The available data indicate that, on average, pairs of neighboring cells correlate their subthreshold membrane potentials for as long as 40% of the time, with peaks as high as 80% [7]. Sensory stimulation can further increase this fraction of shared temporal variability [7]. Incorporated within an appropriate statistical framework, these three constraints represent the central assumptions for all the following analyses and derivations.

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[*] Corresponding author. Fax: +1-415-3458455.
Electronic address: andrea@ski.org

We also briefly re-introduce some definitions [1] that will be used several times in the following. The strength of weak pairwise correlations between spike trains is 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) [9]. The subthrehsold correlations are quantified by using the amplitudes of the normalized peaks of the cross correlograms between pairs of subthreshold traces [7]. With the term "high order correlation events," or "unitary events" we refer to synchronous spiking episodes involving neuronal assemblies with more than two cells (triplets, quadruplets, etc.).[1] Finally, with high cortical activity levels we refer to the spiking activity of groups of neurons firing around 30 Hz or more, as commonly happens when neurons are transiently excited by intracortical or external stimulation.

III. LOWER BOUND OF PSTH VARIABILITY

The main statistical tool we will use to derive our proofs is the combinatorial method (CM). This method allows us to simulate the activity of large ensembles of neurons and is based on a very simplified representation of the neuronal dynamics. When looking at the activity of a large pool of cells, we will only consider its spiking activity, intended as a binary process (spiking/no spiking), and we will neglect other degrees of complexity, such as ionic currents, synaptic dynamics, dendritic morphologies, etc.

A. Main features of the combinatorial method

As a first approximation, the combinatorial method can be thought of as a way to generate raster plots, which are graphical tools, with a matrixlike structure, to visualize the spiking activity of groups of neurons [10]. In the binary version of these plots, the occurrence of a spike by a given cell at a given time is represented by a "1" in the corresponding row (cell number) and column (time bin) of a binary vector (the spike train), and the nonoccurrence by a "0." Thus the whole population's dynamics can be associated to a binary matrix where each row is a binary string associated to a given cell's spike train. Two of three physiological constraints introduced before, C1-C2, can also be described within this binary scheme: high coefficient of variation (CV) of the spiking activity means that the temporal variability of the "1's" in each binary string can be explained by a random process and the weak pairwise correlations between spikes are interpreted as temporal correlations between 1's in pairs of binary strings. We impose that both C1 and C2 constraints are satisfied by spike trains generated by the combinatorial method. Thus, as a built in property, the CM creates large groups of binary strings (of the order of few thousands in the following simulations) respecting the constraints of weak pairwise correlations and coefficient of variation between the binary strings (spike trains). At the same time, we impose that the CM minimizes the degree of high order correlation events. Within this binary scheme, high order correlation events are simply vertical (temporal) alignments of 1's (more than two) along the columns of the binary matrix. Summarizing, the 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 the constraints C1-C2 are satisfied and vertical alignments of 1's (high order correlation events) are minimized. An example is shown in Figs. 1(a) and 1(b) (see figure captions for detailed explanations).

In order to model the dynamics of a large ensemble of neurons by means of the combinatorial method, we will not try to directly generate the whole set of thousands of binary strings (spike trains), but instead we will start with subsets of binary strings, which are characterized by *simpler* high order correlation structures, and consider the overall ensemble as a collection of subsets (also called "blocks" in the following). This procedure will allow us to avoid complicated, in statistical and computational terms, characterizations of the high order correlation properties of large binary matrices, and lets us deal with the easier problem of characterizing the rules of adding together subsets with quantifiable high order correlation structures.

We now describe an appropriate formalism to quantify the statistical features of subsets of spike trains generated by the combinatorial method. Within this formalism, we introduce a theorem concerning the high order correlation properties of the subsets.

We denote with $P^r_{n_s,n_o}$ the maximum number of binary strings (spike trains), containing each n_s 1's (i.e., n_s spikes), and with n_o intersections (of 1's) between any pair of strings, i.e., n_o correlated spikes. r denotes the maximum number of 1's aligned in time, what we call the *order* of the *block* (i.e., group of spike trains thus generated), see Fig. 1. The maximum number of strings for a given order r depends on the combinatorial possibilities to assign spikes according to C1-C2. In the example of Fig. 1(a), $n_o=2$, $n_s=6$, and $r=2$, and $P^2_{6,2}=4$. More in general, for a block of order 2 the following relationship holds true: $P^2_{n_s,n_o}=\text{floor}[(n_s/n_o)+1]$. As shown in the example of Fig. 1(a), after $P^2_{6,2}=4$ strings, there are no more combinatorial possibilities to add strings accordingly to C1-C2 without affecting the order, and the problem is mapped to a high order [$r=3$, Fig. 1(b)].

We denote with $S^\gamma_{n_s,n_o}$ the sub-block of strings of the block $P^\gamma_{n_s,n_o}$, which induces a transition from the order $\gamma-1$ to γ, γ being a positive integer. For example, the sub-block of Fig. 1(b) induces a transition from the order 2, Fig. 1(a), to the order 3. Concerning the order of the sub-blocks, it is possible to prove the following results:

Theorem 1. For a system created by the combinatorial method, the following inequality between sub-blocks must hold: $S^{r+1}_{n_s,n_o} \leqslant S^r_{n_s,n_o}$. ■

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[1] This is not the formal definition of unitary events or high order correlation events (typically considered two distinct concepts), as found in the literature, e.g., Refs. [4,11]. The use of this *simplified* definition allows us to keep the formalism and derivations simple. In the Discussion we will reconcile our definition with more classical ones.

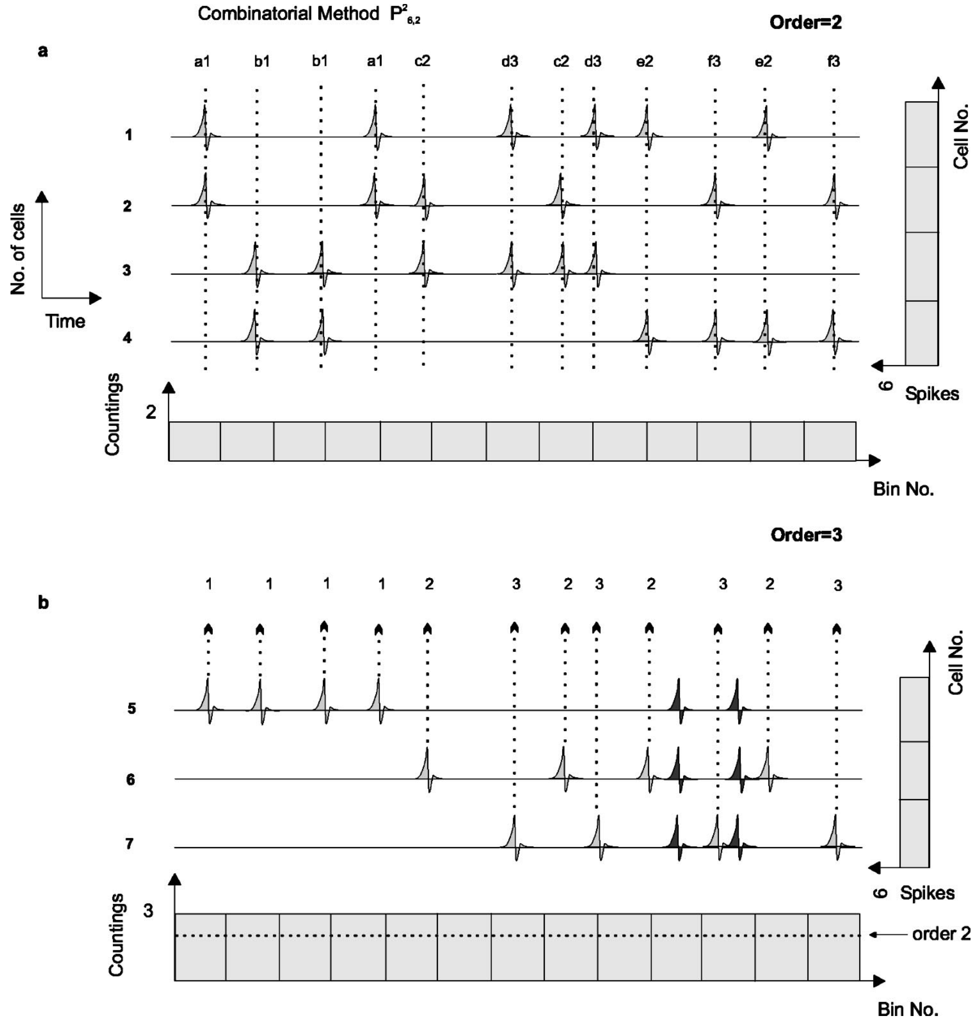

FIG. 1. Combinatorial method: (a) Example of a $P^2_{6,2}$ system. The letters at the top indicate the best combinatorial choices to guarantee that the C1 and C2 constraints are respected. For example, "*f*" indicates pairwise correlations between cells 2 and 4, "*d*" between cells 1 and 3, "*e*" between cells 1 and 4, and so on. When more than four spike trains (the maximum number of trains allowed by the combinatorial possibilities) are created according to the preceding rules, the maximum number of spikes vertically aligned (as shown by the histogram at the bottom) increases to 3 (order=3), panel (b). The numbers at the top of the sub-block of order 3 (i.e., cells numbered 5, 6, and 7), indicate the possible combinatorial strategies to guarantee pairwise correlations with the sub-block of cells in panel (a). For example, the four spikes in cell number 7 (labeled with the number "3") are associated to the spikes d3 (for correlations with cells 1-3) and f3 (for correlations with cells 2-4) in panel (a). Thus, for cell number 7, pairwise correlations with all the cells in panel (a) are created, and two more "free" spikes (indicated in dark gray) are available to generate pairwise correlations with the remaining cells (5 and 6) in the same sub-block.

Proof. Every time a new sub-block is added to a group of spike trains, increasing the order from r to $r+1$, the number of available 1's, $n_{s'}$, to create internal correlations within the newly added sub-block [dark gray spikes in Fig. 1(b)] necessarily decreases in respect to previous sub-blocks, since a nonzero fraction of spikes in the $r+1$ sub-block are "frozen" for the correlation constraints with the previous sub-block [Figs. 1(a) and 1(b), vertical broken arrows]. Since the number of possible spike trains per sub-block is proportional to the combinations

$$\binom{n_{s'}}{n_0}, \text{ with } n_{s'} < n_s, \text{ then } S^{r+1}_{n_s,n_o} \leqslant S^{r}_{n_s,n_o}.$$

The equality can hold when the number of available spikes is high compared to n_o. ■

In other words, the statistical property of the sub-blocks created by the CM, as highlighted in Theorem 1, follows from a simple combinatorial observation: the combinatorial possibilities available to arrange spikes, while respecting the constraints C1-C2, decreases with increasing number of spike trains. As a lemma, Theorem 1 also implies that if we add together two CM sub-blocks of equal size, the order γ of the sum must increase at least by a factor of 1 in respect to the order of the component sets. This is a first important result for the following derivations, since our aim, as mentioned before, is to simulate the overall population dynamics as a collection of smaller blocks with simple, quantifiable high order correlation properties.

B. Compatibility of the combinatorial method with the C3 constraint

Key properties of CM blocks are their compatibility with the constraints C1-C2, while at the same time, by using a combinatorial strategy, the degree of high order correlation events is minimized. The next two lemmas verify the compatibility of CM systems with the last constraint, C3, about the subthreshold correlations.

Lemma 1. For a group of spike trains created by the combinatorial method, the maximum and minimum fraction of time during which two cells can be correlated, are given by $T_f = 1 + \Delta t_{dec} f \times (c_s - 2)$ and $T_u = f \Delta t_{corr} \times (c_s + 2) - 2f \Delta t_{dec}$, respectively.

Proof. The proof follows closely the proof of Theorem 3 in the companion paper [1]. We sketch here only the bottom line of the reasoning and refer the interested readers to the lengthy proof in the companion paper [1]. For a given couple of spike trains, it is possible to define c_s, the pairwise correlation strength between the spike trains, Δt_{dec} a decorrelation time between the subthreshold membrane potentials related to the refractoriness of the spiking activity, Δt_{corr} a correlation time, centered on spike timings during which the subthreshold membrane potentials of any two given neurons could be correlated, and f the mean firing rate; from these quantities it is possible to derive an estimate of the maximum and minimum fraction of time during which the subthreshold membrane potentials of two cells can or cannot be correlated, i.e., T_f and T_u. The new starting equations, following the proof of Theorem 3 in the companion paper, are

$$T_f = \frac{t_{\mathrm{ISI}} - 2\Delta t_{dec}}{t_{\mathrm{ISI}}} + \Delta t_{dec} f_{c_s} \quad T_u = \frac{2\Delta t_{corr} - 2\Delta t_{dec}}{t_{\mathrm{ISI}}} + \Delta t_{corr} f_{c_s}.$$

Considering that the constraint C1 about high coefficient of variation is respected, the time between two spikes (inter spike interval) is $t_{\mathrm{ISI}} = 1/f$ and the time between two correlated spikes for any given pair of neurons, is $T_c = 1/f_{c_s}$. The results follow simply by working out the mathematics. ■

By comparing these estimates with experimentally determined values, it is possible to derive the following:

Lemma 2. The order, r, of any block produced by the combinatorial method, which obeys the constraints of weak pairwise correlations and high CV (C1-C2), is an underestimate of the amplitude of unitary events in cortical networks.

Proof. Using the results of Lemma 1, we plot in Fig. 2 the dependence of T_u and T_f (quantifying the lower and upper tails of subthreshold correlation strength's distribution, as in C3 [7]) on the set of parameters (Δt_{corr}, Δt_{dec}, f, c_s) and we check if there is ever compatibility with reported experimental values (C3). When $f \geqslant 30$ Hz (*high input* regimes), $\Delta t_{corr} > 10$ ms (reported values are around 40 ms [7]) and $\Delta t_{dec} \leqslant 5$ 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 subthreshold correlation strength's distribution, C3 [7] [see also Figs. 1(d) and 2(b) in Benucci *et al.* [1]]. This result about the incompatibility of CM and the constraint C3 is not a proof of Lemma 2 since *incompatible* does not mean *lower order.* To prove the proposition of Lemma 2, we are going to show that the source of incompatibility is related to the *combinatorial nature* of the algorithm. The very "sparse" (but not random) distribution in time of the spikes is what causes the disagreement between CM systems and C3. As soon as some degree of temporal alignment is allowed, the third constraint is satisfied. We use a numerical simulation to show this point:

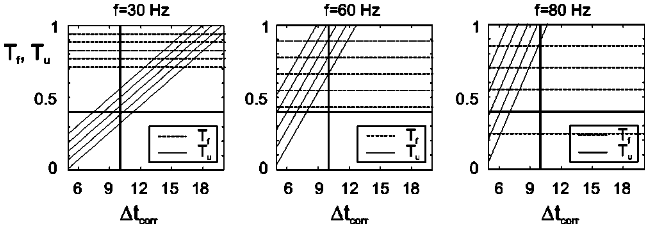

FIG. 2. The three panels show the behavior of T_f and T_u as a function of Δt_{corr} for three different values of the mean firing rate: 30, 60, and 80 Hz, from left to right, respectively [see also Fig. 2(d) in the companion paper [1]]. The five different horizontal and oblique lines refer to T_f and T_u, respectively, while Δt_{dec} changes from 1 to 5 ms (1 for the top line and 5 for the bottom line). The thick vertical line indicates a commonly reported Δt_{corr} value for pairwise correlations in the spiking activity, 10 ms, e.g., Ref. [6], much shorter than for subthreshold correlations, which is typically around 40 ms [7]. The thick horizontal line indicates the mean value for the distribution of the subthreshold correlation strength as found in Lampl *et al.* [7].

Numerical simulation: We refer here to the results of the numerical simulation as shown in Fig. 3 in the companion paper [1]. The underlying rationale is to compare two ensembles of spike trains, uncorrelated Poisson spike trains and a group of spike trains created using an algorithm that allows a higher degree of high order correlation events [1]. We then computed the T_f parameter, which can be related to the subthreshold constraint C3; its numerical value agrees with experimental data only in the latter case, when significant temporal alignments of spikes are allowed. 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 CM and C3 is the "pathological" absence of temporal alignments for all those systems produced by the combinatorial method. Some increased degree of temporal alignments, of a magnitude which must be higher than the by-chance level of correlations observed in Poisson spike trains, is necessary to enter in a physiologically plausible range. ■

Thus Lemmas 1 and 2 prove not only that CM blocks are not compatible with the constraint C3, but also that the degree of temporal alignments in the spiking activity of such blocks is an underestimate of the cortical one. This is an important result for our derivations: the lemmas are suggesting (see the following proofs) that if we simulate the population dynamics putting together blocks created by the combinatorial method, the resulting spiking dynamics is compatible with the cortical one only for what concerns the constraints about the coefficient of variation and weak pairwise correlations, but not for the high order correlation prop-

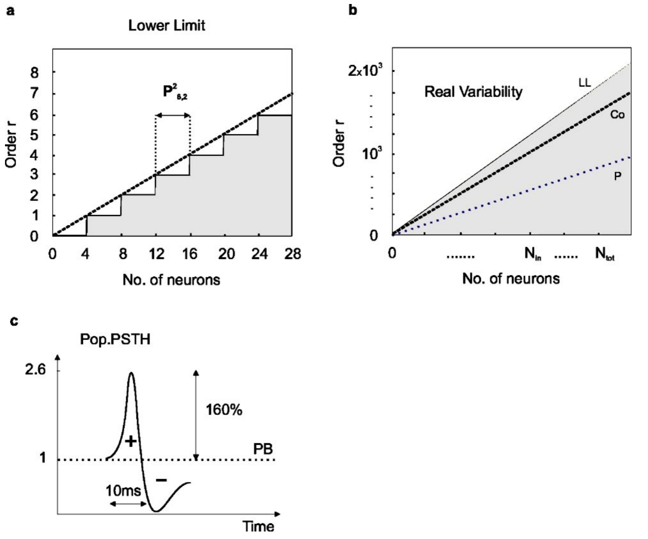

FIG. 3. Lower bound. (a) Step function indicating the relationship between the total number of cells in the network and the order r of the unitary events in the lower bound condition. The dotted line is the linear fit of the step function. This specific example relates to the block of spike trains shown in Figs. 1(a) and 1(b). (b) Schematic plot of the relationships between the total number of neurons and the order r for the different methods. The shaded area represents the part of the plane associated to systems with variability lower than the cortical one (see text). The total number of neurons is related to the order of the system (the magnitude of the unitary events) via a linear function, whose slope changes accordingly to the generating method: P, Poisson; Co, combinatorial. The function associated to the combinatorial method is obtained by linearly interpolating the step function in (a). The 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 level (lower bound condition). **(c)** Variability of the population PSTH in the lower bound condition (spiky curve) vs the Poisson case (horizontal line). Since the integral of the two superimposed PSTH's is the same, a positive peak (+ sign) in the lower bound condition, with a 160% increase from the Poisson background (PB), must be associated with a negative peak (− sign) of equivalent area. The PB is normalized to "1" for simplicity. The time duration of the unitary event is around 10 ms (see text).

erties. CM systems minimize temporal alignment of spikes thus underestimating the magnitude of cortical unitary events. Note that we do not know what their magnitude is, but we have been able to go around the problem focusing on the subthreshold correlations and showing that temporal correlation properties in CM systems are too "simple" to assure the compatibility with the constraint C3.

C. A lower bound for the unitary events in the cortical dynamics

Using the result of the two lemmas, we now show it is possible to create an arbitrary large population of spike trains, whose high order correlation structure underestimates the degree of high order correlation events existing in an equally large ensemble of cortical neurons. We will use blocks of strings of *order 2* as building blocks to create an ensemble of spike trains with a negligible high-order correlation structure. Since blocks of order 2 are easier to handle, we will be able to quantify the degree of high order correlation events for an arbitrary collection of blocks, and, thanks to the results of the lemmas, we can be sure that the emerging high order correlation structures underestimate the cortical ones, thus defining the lower bound we are looking for.

Considering a group of spike trains as a sum of several second order distinct blocks, we make the following assumptions: instead of imposing that *any* two spike trains in the system have the same correlation strength, we simply require that the trains in the same second order block are correlated according to a given n_o parameter, while for the correlations between trains not belonging to the same block we require a weaker correlation strength, according to a new parameter $n_{o'} \ll n_o$, which is a "small" nonzero integer ($\geqslant 1$). This is a strong simplification also in respect to electrophysiological data. Indeed, the parameter $n_{o'}$ represents a sort of "decorrelation" factor between the blocks in the sense that it further reduces the previously assumed weak pairwise correlations within the blocks. Thus this parameter sets the average correlation strength to lower values than those physiologically observed. It is now possible to formulate the following.

Theorem 2. A step function, of step width $P^2_{n_s,n_o}$, and step height 1 is a lower bound for the amplitude of higher-order events in the cortical dynamics.

Proof. Given an initial block with as many as $P^2_{n_s,n_o} = \mathrm{floor}(n_s/n_o+1)$ strings, the size of the following block is less than, or equal to, the size of the first block (Theorem1). According to Lemma 2, each block underestimates the magnitude of unitary events in the cortical dynamics. When more blocks are added together, there is another underestimate of the temporal correlations between the spikes due to the fact that $n_{o'} \ll n_o$, as in the assumptions. If nonzero correlations are considered, as in the present case, the order r must increase at least by 1 every time a block is added. This way, by always adding second order blocks it is possible to get a step function, of step length $P^2_{n_s,n_o}$ and step height 1, which relates the number of strings in the system (the population's size) to the order of the block; see Fig. 3(a). This step function is produced accordingly to constraints that carry underestimates of the cortical variability of two types: *intrinsic* (within each block, Lemmas 1 and 2) and *extrinsic* (when blocks are put together), thus defining a lower bound for cortical unitary events. ■

Note that the slope obtained with $P^2_{n_s,n_o}$ *might not be the steepest one;* see Fig. 3(b). A step with decreasing length (Theorem 1), for example, would produce a steeper behavior. In other words, we have described a system (the group of spike trains generated summing together blocks of order 2), which underestimates the degree of high order correlation events of an equivalently large ensemble of spiking neurons, with the same second order correlation properties. Thought we do not know the magnitude of this underestimation; for this reason we talk about a lower *bound* and not about a lower *limit*.

D. Variability in the lower-bound condition

So far, we have shown the two following results: (i) we derived a quantitative expression (the step function of Theorem 2) to relate the degree of high order correlation events in a group of spike trains generated by the combinatorial method, to the population size. (ii) We have shown that given an equivalently large ensemble of spike trains, the degree of high order correlation events in CM systems must be lower than in the cortical case.

We now quantitatively address the statistical significance of these results and show that in ensembles produced by the combinatorial method, unitary events are a preponderant dynamical phenomenon. It follows that the same conclusion must apply (even more convincingly according to Theorem 2) to the cortical dynamics.

To quantify the statistical significance of unitary events in CM systems we use, as a reference level, uncorrelated Poisson spike trains with the same average firing rate and CV; see Figs. 3(b) and 3(c). This choice is very natural: if correlations are not relevant for the information processing and they simply occur *by chance*, then uncorrelated Poisson spike trains are the simplest level of description of the dynamics [10].

The first step is to show that CM systems have a degree of temporal correlations that is higher than in the Poisson case: given an ensemble of spike trains generated by uncorrelated stationary Poisson processes (with constant mean rate f), the average number of spikes per time bin Δt_{bin} is given by $(n_s/N_{bin})\times N_{in}$ [expression on the right side of the following Eq. (1)], where N_{in} is the total number of spike trains, n_s is the number of spikes per each train ($n_s=f\times T$), and N_{bin} is the number of "bins" used to discretize the time window of analyses T, i.e., $N_{bin}=T/\Delta t_{bin}$. If instead the group of spike trains is a sum of blocks of order 2, as in the lower bound conditions, a linear relationship between N_{in} and the order of the unitary events can be obtained by linearly interpolating the step function of Fig. 3(a) [broken line, and expression on the left side of Eq. (1)]. Thus the two systems (Poisson and CM) would have the same order r if the following equation is satisfied:

$$\frac{1}{\mathrm{floor}\left(\dfrac{n_s}{n_o}+1\right)}\times N_{in}+2=\frac{n_s}{N_{bin}}\times N_{in}. \qquad (1)$$

Working out the mathematics and making few simplifications (i.e., omitting the "floor" function and considering that $n_s/n_o+1\cong n_s/n_o=10$, for $c_s=0.1$), the equation has a solution iff $n_o\times N_{bin}<n_s^2$. As pointed out before, we are interested in correlations during high input regimes therefore by using 35 Hz for the average firing rate, $c_s=0.1$ and $\Delta t_{bin}=1$ ms, with a time window of analysis $T=1$ sec ($N_{bin}=1000$), the equation has no solution. This result does not depend on the time-window duration, as can be seen by changing the variables $n_s=\langle f\rangle\times N_{bin}\times\Delta t_{bin}$ and $n_o=\langle\tilde{f}\rangle\times N_{bin}\times\Delta t_{bin}$, with $\tilde{f}=f/10$, since we fixed c_s to 0.1. N_{bin} then cancels out in the inequality, which can be rewritten as $\langle f\rangle>1/(10\times\Delta t_{bin})$. The inequality is satisfied only for average firing rates above 100 Hz. Even considering only groups of cells being optimally activated ($\langle f\rangle=80$ Hz), the equation still has no solutions. Thus these results show that in the correlated (lower bound) case, there must be temporal alignments of spikes (high order correlation events) of larger amplitude than in the uncorrelated Poisson case (reference system).

We need to make the comparison between the two methods, Poisson and combinatorial, more quantitative. In this respect we can use two analytical approaches: one working at a *local* level, meaning at the level of the building blocks of CM systems, and another one at a *global* level, considering the whole population of spike trains.

Local level: due to the pairwise correlations, the building block of the step function, $P^2_{n_s,n_o}$, 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 in the Poisson case $r=(n_s/N_{bin})\times N_{in}$ and using $N_{in}=P^2_{n_s,n_o}=n_s/n_0+1$ (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 is higher than 2 only for firing rates higher than roughly 200 Hz. Thus already at the level of the individual building blocks the two systems have different degrees of high order correlations; difference that intuitively should *sum up* when blocks are added together. This is shown in the next analyses.

Global level: considering the (N_{in},r) plane as in Fig. 3(b), a linear relationship between the total number of neurons in the population and the order of the vertical alignments of spikes (high order correlation events) can be computed for both the Poisson and the combinatorial methods. For the Poisson case we showed before that $r=(n_s/N_{bin})\times N_{in}$, and given that $n_s=\langle f\rangle\times N_{bin}\times\Delta t_{bin}$, 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 for n_s as above, then $r=N_{in}/(1/c_s+1)+2$. Using $N_{in}=10^4$, $c_s=0.1$, $f=35$ Hz, and $\Delta t_{bin}=10^{-3}$ sec, we obtain 350 and 911 for the value of r, in the Poisson and combinatorial cases, respectively.

More in general, a quantitative comparison can be carried out by evaluating independently the two expressions of Eq. (1). Using $N_{in}=10^4$, $n_0=3$, $n_s=30$, and $N_{bin}=10^3$ (i.e., $\langle f\rangle=30$ Hz and $c_s=0.1$) gives a 160% fractional increase of unitary events' magnitude in the CM case, in respect to the Poisson background [Fig. 3(c)]. The percentage is still significant, 22%, even for the extreme case of a much smaller, very active population of neurons, $N_{in}=300$, $n_0=8$, $n_s=80$ (i.e., $\langle f\rangle=80$ Hz and $c_s=0.1$). The relative independence of the fractional increase from the parameter N_{in} is due to the fact that for typical values of the parameters $N_{in}\times n_o/n_s\gg 2$, then N_{in} can be canceled out in Eq. (1). Instead, the absolute magnitude (order) of the unitary events strongly depends on the precise value of N_{in}, ranging from 911 to 29, for N_{in} equal to 10^4 and 300, respectively.

Finally, for what concerns the duration and frequency of occurrence of the unitary events, they can be quantified according to the following considerations: referring to Figs. 1(a) and 1(b), all the spikes in a given spike train can be possible points in time for the emergence of unitary events.

Since in CM systems spike trains are generally only partially overlapping, but never nonoverlapping (C2), it is reasonable to expect $[\langle f\rangle, 2\times\langle f\rangle]$ as a range for the frequency of occurrence of high order correlation events. Moreover, since unitary events can be considered as the *generators* of the pairwise correlations, their duration must be related to the width of the experimentally measured cross correlograms, i.e., few milliseconds time scale (as it has also been shown in simulation studies [12,13]).

The take home message from these qualitative and quantitative comparisons is that CM systems are characterized by a degree of high order correlation events that is significantly higher than what is found in uncorrelated Poisson spike trains with identical second order correlation properties. What traditionally defines high order correlation events or unitary events is the statistical significance in respect to dynamical systems where spike correlations occur by chance and have no functional meaning. Thus the highly statistical difference found with the above quantitative analyses reconciles our definition of unitary events with more standard ones, e.g., Ref. [11]. Most importantly, the finding that high order correlation event are a preeminent phenomenon in the dynamics of CM systems, in conjunction with the results of Theorem 2, finally prove that high order correlation events are a key dynamical feature of the cortical dynamics.

IV. CONCLUSIONS

In this study we described the correlation properties of large ensembles of neurons in the millisecond time scale. We showed that, under very general conditions (C1-C3), unitary events appear in the cortical dynamics.

Despite the fact they have never been observed due to technical limitations or deduced theoretically in an undisputable way, unitary events appeared in the theoretical discussion since 1963 with Griffith [14] 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, “high order events,” “volleys,” “barrages” of inputs, “conspicuous coincidences,” “unitary events,” “population spikes,” or “large brief excitatory events” [4,11,12,15–19].

Unitary events have been claimed as extremely interesting from the point of view of information coding, e.g., Ref. [3]. The crucial importance of proving their existence in cortical networks is easily understood by considering that the large majority of theoretical models based on correlation require, as a *working hypothesis*, the existence of high order correlation events in the network’s dynamics. Assumed to exist in “synfire chains” [4], they are meant to play a crucial role 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., Ref. [5].

The scope of the results found is not limited to the method used. The logic behind our approach has been to identify one specific method (the CM) which allowed us to simulate neuronal dynamics with two requirements: (i) underestimate the degree of high order correlation as observed in the cortical networks, (ii) provide and explicit quantitative way to evaluate the magnitude of unitary events. Any other model fulfilling such requirements could have done an equally good job. Different analytical relationships could have eventually been found, together with more accurate estimates of the lower limit, though complementary, and not in contradiction with our results. This idea can also be understood graphically by looking at Fig. 3(b): we picked one specific function defined in the shaded part of the plane, below the level of cortical high order correlation events. Many other functions with different analytical properties can possibly be defined in this subspace, though their existence would not “shift” CM systems into a different part of the plane, i.e., more comprehensive analyses could complement our results but not invalidate them.

The results are robust also in respect to the experimental assumptions. The three physiological constraints considered in the assumptions are sufficient conditions (and perhaps necessary as well) to prove the validity of the results. Thus any other experimental evidence consistent with these well established constraints cannot invalidate the results.

In conclusion, this study provides a formal demonstration that unitary events must and do appear in the constrained population dynamics, to an extent which is related to the computed lower bound. These results add interesting insights about how information flows in cortical networks, and strongly supports coding strategies based on correlation schemes. Advances in recording techniques are needed for a final experimental validation of these findings.

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