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Pooled spike trains of correlated presynaptic inputs as realizations of cluster point processes

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Abstract. The pooled spike trains of correlated presynaptic terminals acting synchronously upon a single neuron are realizations of cluster point processes: the notions of spikes synchronizing in bursts and of points bunching in clusters are conceptually identical. The *primary processes* constituent specifies the timing of the cluster series; *subsidiary processes* and *poolings* specify burst structure and tightness. This representation and the Poisson process representation of independent terminals complete the formal approach to pooled trains. The notion's usefulness was illustrated by expressing physiological questions in terms of those constituents, each possessing a clear biological embodiment; constituents provided the control variables in simulations using leaky integrate-and-fire postsynaptic neurons excited by multiple weak terminals. Regular or irregular primary processes and bursts series determined low or high postsynaptic dispersions. When convergent set synchrony increased, its postsynaptic consequences approached those of single powerful synapses; concomitantly, output spike trains approached periodic, quasi-periodic, or aperiodic behaviors. The sequence in which terminals fired within bursts affected the predictee and predictor roles of presynaptic and postsynaptic spikes; when inhibition was added, EPSP and IPSP delays and order were influential (summation was noncommutative). Outputs to different correlations were heterogeneous; heterogeneity was accentuated by conditioning by variables such as DC biases.

1 Introduction

Correlations between presynaptic terminals are critical in convergent arrangements where presynaptic terminals act upon the same postsynaptic neuron. Formal approaches and simulations have been specially useful for understanding them (e.g., Brunel and Sergi 1998; Burkitt 2001; Burkitt and Clark 2001; Feng and Zhang 2001; Fourcaud and Brunel 2002; Fujii et al. 1996; Hohn and Burkitt 2001; Moreno et al. 2002; Rudolph and Destexhe 2001; Salinas and Sejnowski 2000, 2002; Schneidman et al. 2003; Segundo 1970; Segundo et al. 1968; Shadlen and Newsome 1995; Softky and Koch 1993; Svirskis and Rinzel 2000).

This communication argues for the thesis that the pooled spike trains of correlated converging presynaptic terminals are realizations of cluster point processes. Furthermore, using the thesis as guide to simulations based on a simple model of weak synchronous converging terminals, it illustrates its biological potential. The questions targeted concern the output spike trains associated with weak excitatory terminals that correlate in several ways; these questions are not trivial and remain incompletely answered. Involved are regular or irregular synchrony-inducing referent events, increasing or decreasing presynaptic terminal synchronies, delays and order generally and when both EPSPs and IPSPs are present, and, finally, how correlation effects are conditioned by other variables (say, DC biases).

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2 Thesis

The thesis is that the pooled or total spike trains of correlated presynaptic terminals are realizations of cluster point processes. This section identifies the targeted biological situation (Sect. 2.1), defines cluster point processes (Sect. 2.2) and argues the case (Sect. 2.3).

2.1 Convergent synaptic arrangements. Total or pooled spike trains

2.1.1 Convergent arrangement description. Figure 1a depicts synaptic arrangements involving single postsynaptic neurons, sorting them by individual synaptic strengths a and numbers N of terminals (e.g., Shepherd 1998). Sorting is schematic because categories overlap, and many individual neurons may involve several. Moreover, synaptic strengths reflect the induced conductance changes: their common representation by PSP amplitudes a (which,

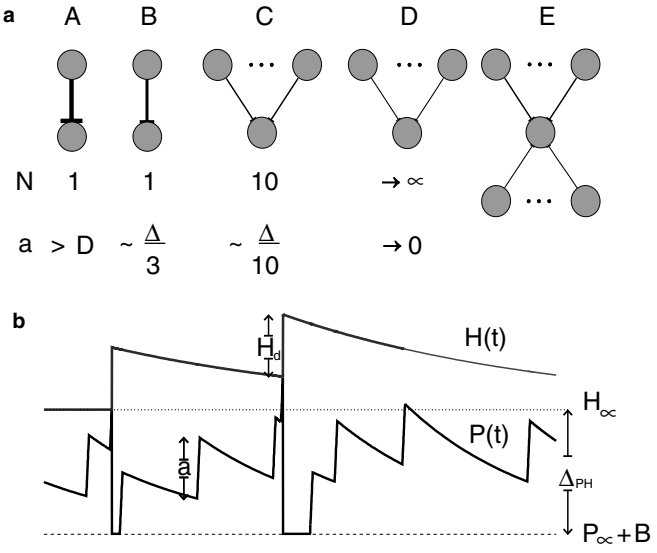

Fig. 1. **a** Synaptic arrangements (schematic). A–D: categories with increasing numbers N of presynaptic terminals and decreasing PSP sizes a (adapted from Segundo et al. 1968). C, D: convergent arrangements with multiple weak terminals and, respectively, small or minute PSPs. E: simulated preparation combining categories C and D. **b** Leaky integrate-and-fire postsynaptic neuron model. Membrane potential $P(t)$ (time constant τ_P; asymptote P_∞). Threshold $H(t)$, time constant τ_H; asymptote H_∞. EPSP amplitude a. Spikes occur when $P(t)$ reaches $H(t)$. Resetting after spikes: $P(t)$ to $P_\infty + B$; $H(t)$ to $H(t) + H_d$

as currents, depend on transmembrane voltages), though defensible, is an oversimplification.

Figure 1a-C, D, E represent the convergent arrangements discussed here: multiple presynaptic terminals act directly upon the postsynaptic neuron and elicit weak synaptic effects (Sect. 2.3).

Convergent arrangements pervade neural networks: examples are "Ia afferents-dorsal spinocerebellar tract neurons," "parallel fiber-Purkinje neuron," and others (e.g., Mendell and Henneman 1971; Softky and Koch 1993; Shadlen and Newsome 1995; Fujii et al. 1996; Salinas and Sejnowski 2000; Chen and Shepherd 2002). Moreover, they play critical roles in neural transactions. Each terminal (called #1, . . . , #j, . . . , or #N) generates a spike train that drives the shared postsynaptic neuron. The weak effects (conductance changes, currents, potentials) of individual spikes in some terminals can be recognized by the naked eye in conventional records; others demand spike-triggered averages or simultaneous activation of many. The union of all N individual or "component" presynaptic spike trains will be called "total" or "pooled" spike trains: intervals between one spike and the next, i.e., of the first order, are between points in the same or separate components and need not have lower bounds.

2.1.2 Correlations. Correlations between spike trains in separate neurons pervade neural operations. Spike trains "correlate" when, at certain times relative to a spike in one train, the other train tends to have more than average spikes or less; they are independent otherwise. Correlations have been reported in practically all fields; indeed, since neurophysiology's beginnings, abundant publications (from textbooks to specialized papers) tell us that neurons performing specific tasks not only generate individually suitable trains but also work together with others, firing or not firing close in time or at subtly staggered delays. Indeed, firing coincidences, anticoincidences, and/or orderings play prominent roles in many kinds of neural coding that match referent events and specific neurons (e.g., Abeles 1991; Caputi 1999; Eckhorn et al. 1990; Wilson et al. 2004).

This happens in sensory neurons whenever appropriate stimuli arrive (taps, vibrations, electric organ discharges, etc.) and in effector neurons when driven by commands from higher centers including pattern generators (agonist motoneurons during twitches, respiratory neurons during breathing, etc.). Multicell correlations exist also in cortical networks when, say, animals perform learned delayed-pointing tasks, thus proving the existence of functioning cell assemblies and intrinsic synch-chains (Villa et al. 1999).

Correlations alluded to here will be those where neurons tend to fire close in time, thus "synchronously," and in particular orders. In such cases, if one used a single electrode to record from all neurons, the total or pooled spike train would exhibit bursts and bursty patterns. "Bursts," as used here, has the sense that is traditional in neurophysiology, namely, sets of spikes tightly packed in time separated from other such sets by longer intervals. Requiring the bracketing of shorter interval runs by longer intervals, with an obvious functional importance in, say, breathing, chewing, etc., has a sound physiological rationale.

Germane to the argument is that referent events, and thus bursts, recur, composing series along time. The timings of such series reflect those of, for example, stimulus deliveries, needs for particular acts, learned task components, and so forth. Possible timings therefore are numerous; they are, moreover, highly heterogeneous, exhibiting an enormous variety of averages arising from every few seconds to very frequently every few milliseconds and exhibiting patterns from highly periodic and predictable to highly aperiodic and unpredictable. In, say, auditory nerve fibers, bursts in noisy environments or listening to 1-kHz tones will arise, respectively, irregularly at intervals of up to seconds or regularly every 1 ms. Terms applied to series of events have the precise senses defined earlier (Segundo et al. 1966, 1968). "Timings" are the increasing sets of instants when events occur. "Pattern" refers to the dispersion and sequence of the point process. Patterns plus averages (rates, intervals) describe timings fully.

The same neuronal sets whose spike trains in natural operation correlate can also behave independently. Independence holds particularly during unvarying conditions (e.g., Durbaba et al. 2003), for example, in sensory coding of constant length and contraction by Ia afferents from muscles and in motor coding by motoneurons when the "desired" outcome is a constant muscle length. Thus, independence also has a place in neural coding. Schneidman et al. (2003) have discussed independence and correlation

in neuronal ensembles that code (or decode) sensory signals in the presence of noise. They propose (and compare with others) a conceptual framework composed by different situations: "activity related" situations involve correlations between cells, regardless of stimuli; "conditional" situations involve correlations that separately depend on signals and noise; "information" situations involve how much more one knows about stimuli when observing joint responses than by summing the individual contributions, thus cell "synergies".

Correlations (and independence) exist also in converging arrangements, where they affect postsynaptic outputs. In vivo analyses of convergent arrangements pose technical difficulties (e.g., multiple controls and monitorings): hence, understanding them has come largely from formal approaches. It was in fact work with physiologically plausible models and simulations that first proved the importance of correlations and the kind of correlations, as opposed to independence, in determining the output neuron's behavior (Segundo et al. 1968; Segundo 1970); formal approaches and analyses in specific networks confirmed and extended these findings (e.g., Softky and Koch 1993; Shadlen and Newsome 1995; Fujii et al. 1996; Salinas and Sejnowski 2000; Svirskis and Rinzel 2000; Burkitt 2001; Feng and Zhang 2001; Hohn and Burkitt 2001; Rudolph and Destexhe 2001; Moreno et al. 2002). Hence, correlations (and independence) contribute to the code that summarizes synaptic codings, i.e., the relation between presynaptic and postsynaptic spike trains. Separate converging terminals can differ operationally because, taken either individually or in subsets, they have dissimilar sources, special postsynaptic effects, etc. For instance, separate Ia afferents act differently on single dorsal spinocerebellar tract neurons (Henneman et al. 1974). Distinctness implies the relevance of when and how many times each terminal fires in the burst. Accordingly, one must worry about where each spike cames from, retaining terminal individuality.

2.2 Spike trains as point processes

Spike trains in individual neurons are series of events studied as point processes along time. The present considerations are largely based on Cox and Isham (1980) and Cox and Lewis (1966); references to them, though often omitted for brevity, are implicit throughout. Stationarity will be assumed unless specifically noted.

2.2.1 Sets of neurons. Total spike trains. Pooled point processes. A point process obtained by superposing individual point processes and ignoring where each point came from is called a "pooled point process." When dealing with representations of convergent spike trains it is legitimate to ignore initially that points may come from separate components, assigning all to a single class and studying the total train as a "univariate" point process. The counts and average rates of a pooled process are the sums of those of its components. An assumption, useful and also plausible with convergent spike trains, is that all individual components #1, ... , #j, ... , or #N have average rates $\{m_1, \dots, m_j, \dots, m_N\}$ close to the same value m ($m_1 \approx \cdots \approx m_j \approx \cdots \approx m_N \approx m$); their average intervals, $\{T_1, \dots, T_j, \dots, T_N\}$ are close to T ($T_1 \approx \cdots \approx T_j \approx \cdots \approx T_N \approx T$). Subscripts will indicate the respective components, so labeled because of the order in which they tend to fire (Sects. 2.3 and 3.1.1). All point processes are defined from a time origin at the first event to the last; such processes are known as "ordinary" and the sampling as "synchronous" (Cox and Lewis 1966; Cox and Isham 1980). Hence, $m_j = 1/T_j$ and $m = 1/T$. The pooled mean rate is $M = \sum_j m_j \approx Nm$ with j going from 1 to N. The pooled mean interval is $I \approx T/N$ with $M = 1/I$.

As noted, it may not be legitimate to always ignore the fact that components differ; component individuality must be retained and each point assigned to a particular category. The pooled process is treated as "multivariate." This clearly applies when targeting convergent arrangements where terminals, arising in different neurons and/or acting through different synapses, often have different roles.

2.2.2 Relevant spike train statistics. Both bursts and the bursty spike trains that include them in significant numbers are represented by point processes with characteristic features. Statistics relevant to simulations will be mentioned. The intervals of the first order between successive spikes, depending on whether they are within bursts or between them, fall into clearly distinct shorter or longer categories, respectively. Interspike interval histograms (ISIHs) reflect this by modes in clearly distinct categories at small or large values; in the simplest cases, ISIHs are bimodal.

The second-order properties of spike trains can be quantified using auto-intensity functions (AIFs) m_{AA} and autocorrelation histograms (ACHs): these are, respectively, the cross-intensity function and crosscorrelation histogram (defined below) of the series of events A with itself. ACHs of bursty spike trains show around the origin a broad "central" peak, usually with a trough on either side. This peak's profile, height, and width reflect the details of how the different terminals synchronize when composing bursts. If terminals tend to fire at particular instants and particular numbers of times within bursts, the central peak is jagged with secondary narrower peaks and troughs. In simulations, the presynaptic neuron that usually fires the first, ... , jth,... , or Nth is labeled, respectively, #1, ... , #j, ... , or #N (Sect. 3.1.1) and contributes mainly to the similarly ordered peaks. Features around the origin become more marked when spikes exhibit timings consistent from one burst to the next. Away from the origin, additional ACH peaks (with adjacent troughs) may appear: their presence, locations, and features depend on burst consistency as well as on the timing of the series of bursts (reflecting the referent event timing). When bursts vary little and occur at equal intervals, additional peaks are obvious and evenly separated; when bursts vary and arise irregularly, peaks are less noticeable and happen irregularly.

Correlation or independence between separate terminals as well as those between individual terminals and the postsynaptic neuron can be evaluated by several statistics (e.g., Brillinger 1975; Bryant et al. 1973; Conway et al. 1993; Durbaba et al. 2003; Farmer et al. 1993; Oshio et al. 2003; Rosenberg et al. 1989; Rudolph and Destexhe 2001; Schneidman et al. 2003; Svirskis and Rinzel 2000); simulations use the cross-intensity functions (CIFs) and their estimators the crosscorrelation histograms (CCHs). Moore et al. (1966, 1970), Perkel et al. (1967), Bryant et al. (1973), Brillinger (1975), Brillinger et al. (1976), and Lindsey et al. (1989) pioneered their application to spike trains. Bryant et al. (1973) explained the CIF formulae and definitions together with their main properties, extensions, estimations, and interpretations; they also described what they look like in simple circuits (synaptic connections, shared inputs in *Aplysia*).

For simultaneously occurring stationary series of events, e.g., spike trains, A, B, M_{AB} is the expected number of B events in the interval from 0 to $\tau(B(0,\tau))$ with an A event at time 0:

$$M_{AB} = E(B(0,\tau)/A \text{ event at } 0)\,, \tag{1}$$

where E indicates the expected value.

The CIF is:

$$m_{AB} = \frac{d(M_{AB})}{d\tau} = \lim_{\Delta\tau\to 0} \frac{M_{AB}(\tau+\Delta\tau) - M_{AB}(\tau)}{\Delta\tau}\,. \tag{2}$$

The CIF expresses the B rates that exist on the average at each delay τ from an A event. Converted to covariances, CIFs lead to the covariance densities of the counting process; the covariance's Fourier transform defines the spectral density function for the counting process. CIF peaks, troughs, or flatness reveal, respectively, local increases, decreases, or invariance relative to the overall average and thus correlations between A and B; flatness throughout CIF implies that A and B are independent processes. In all practical applications, CIFs become flat at sufficiently long delays; this reflects the finite duration of any physical issue imposing correlations. Moreover, if adjusted by the proportion of the respective averages, $m_{AB}(\tau)$ and its converse CIF $m_{BA}(\tau)$ are symmetric: this reflects that "A precedes B by τ" is equivalent to "B follows A by τ." Full interpretation of m_{AB} and m_{BA} requires knowledge of the AIFs m_{AA} and m_{BB} of the matched processes (Bryant et al. 1973). The CIF concept can be extended to relations involving several presynaptic and/or postsynaptic spikes.

CCHs (CIFs estimators) are histograms of intervals of all orders (the first, second, ...) forward or backward from an A event to a B event. Abscissae or delays τ are the magnitudes of A to B intervals. Ordinates are the average of the B rate at τ from the A event, normalized to per-unit time per reference event. CCHs require selecting bin width and τ range. Another legitimate ordinate is B firing probability. Rigorous confidence procedures that establish whether deviations in a particular CCH are statistically significant exist only for special theoretical cases (Brillinger et al. 1976); therefore, in most instances one relies on empirical criteria such as those identified later.

2.2.3 Cluster point processes. Definition. Constituents. The notion of point processes called "cluster point processes" arose when studying univariate count distributions in fixed sets; it has been applied in, say, cosmology, traffic problems, etc. Cox and Isham (1980) warn that practically all processes whose points tend to form tight sets qualify as cluster point processes that, consequently, compose a heterogeneous broad category. In biology, this need not be a minus for, as Winfree (1980) stresses, natural fuzziness and diversity may be alien to excessive exactitude and restriction. Grüneis et al. (1989) studied cluster point processes extensively and, noting they represent well brainstem spike trains during paradoxical sleep, recognized their importance in spike train analyses.

Cluster point processes are defined by their constituents: (α.) the primary process, (β.) the subsidiary process, and (γ.) an orderly pooling (Cox and Isham 1980; Grüneis and Musha 1986; Grüneis et al. 1989). Each constituent is independent of the others. This argument implies univariate approaches unless explicitly noted; however, when points represent dissimilar components, multivariate approaches are indispensable (Cox and Isham 1980).

α. *"Primary process."* This specifies the timing of points p_k ($k = \ldots -1, 0, 1, \ldots$) called "centers" (Fig. 3a). Assuming a finite number n of centers,

$$\{p_1, \ldots, p_k, \ldots, p_n\}\,. \tag{3}$$

The primary processes can be any point process; accordingly, their series may involve many or few centers, tightly packed or dispersed, occurring regularly or irregularly, predictably or unpredictably (Figs. 2 and 3). At the extremes of this heterogeneous simplicity-complexity scale are highly regular centers and clusters with all interposed intervals practically equal to their average and highly irregular, Poisson-like ones. Simulations represent them by cases called, respectively, "correlated pacemaker" (Fig. 3a) or "correlated Poisson" (Figs. 2b-rasters and 3a).

β. *"Subsidiary process."* A "cluster" is a set of points scattered around a center. Each cluster is identified by its center subindex k. Points $\ldots p_{k,j}, \ldots, p_{k,K}$ are identified by a first subscript k indicating the cluster it pertains to; a second subscript separates the points in each cluster. Points from the same component are assigned the same second subscript j in all clusters.

The subsidiary process imposes the structure of the individual clusters. (i) First, they specify the number of points $0, 1, 2, \ldots$ in each. The kth cluster will have K points (k and K need not relate). Outcome 0 means an "empty" cluster. Emptiness in convergent arrangements implies that a referent event does not associate with spikes in any terminal. Subsidiary processes can stipulate K by assigning to each component a discrete probability density for the number of points it contributes to individual clusters. Thus, subsidiary processes stipulate for each cluster how many components participate and how many points each provides. Empty clusters or the absence of particular components may have physiologically plausible implications. (ii) The subsidiary process specifies also the separations $s_{k,1}, \ldots, s_{k,j}, \ldots, s_{k,K}$ that in each cluster

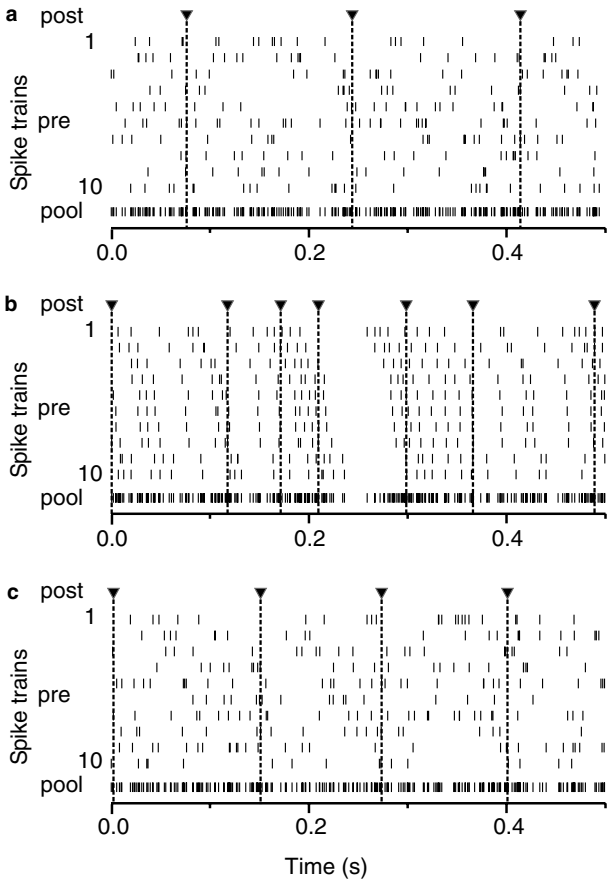

Fig. 2. Rasters of spike trains with different drives. Presynaptic individual spike trains (presynaptic #1, . . . , 10) or pooled (pool). *Arrowheads and vertical lines*: Postsynaptic spikes (post). **a** Independent Poisson spike trains. Pooled spike trains: Poisson point processes. **b** Correlated spike trains imposed by the selected cluster point process. Pooled spike trains: Cluster point processes. **c** Independent shuffled spike trains; shuffling is explained in text (Sect. 3.1.2). Pooled spike trains: Poisson point processes. Simulations with 19.2-mV biases

exist between each of its K points and its center: i.e., $s_{k,1} = p_{k,1} - p_k, \ldots, s_{k,j} = p_{k,j} - p_k, \ldots, s_{k,K} = p_{k,K} - p_k$. They stipulate this by assigning to each component a probability density for the separations of its points from the centers. The densities in separate components determine the sequence or ordering in which their respective points arise along individual clusters: for example, components with predominantly negative separations will tend to precede those with predominantly positive ones. "Sequence" means how components line up in time.

Clearly, subsidiary processes can include many different rules. What follows, based on rules used in the simulations (Sect. 3.1.2), simplifies arguments without changing their conclusions. A first rule is that each component contributes a single point to all clusters; because of this, every cluster has one point from each component and a total of N points ($K \equiv N$). Also, a particular separation probability density is assigned to each component. Densities imposed a tendency for components to appear in a preferred order: the component usually appearing the first, . . . , jth, . . . , or last, is labeled #1, . . . , #j, . . . , or #N (Sect. 3.1.2).

Clusters will be ($k = 1, \ldots, n$):

$$\{p_k + s_{k,1}, \ldots, p_k + s_{k,j}, \ldots, p_k + s_{k,N}\}. \quad (4)$$

Abbreviating $\{p_k + s_{k,j}\}$ by $\{p_{k,j}\}$,

$$\{p_{k,1}, \ldots, p_{k,j}, \ldots, p_{k,N}\}. \quad (5)$$

Examples of subsidiary processes are illustrated by simulated ones in Fig. 3b, one in each column (Sect. 3.1.2). All processes imposed N points in every cluster. Each process imposed upon $s_{k,j}$ a different probability density estimated by the histogram in the bottom row. Rasters of separate clusters in isolation (not yet pooled) illustrate the features of individual clusters and how clusters vary (i.e., consistence).

γ. *"Pooling."* A final superposition of all clusters uses all $p_{k,j}$ (i.e., all k and j) and creates the cluster point process (Fig. 2). Pooling rules stipulate ignoring or preserving the identities of the component process (i.e., #1, . . . , #j, . . . , or #N) and/or of the cluster (i.e., 1, . . . , k, . . . , or n) whence each point came. Rules stipulate also including or excluding centers in clusters and accepting or rejecting cluster overlaps.

The resulting cluster point process has averages (rate, interval) that reflect jointly those of the primary process and the average number of spikes per cluster. Its dispersion reflects that of the primary process, as well as the spreads and numbers implied by the subsidiary process.

The final recovery of component identities (e.g., #1, . . . , #j, . . . , or #N) and use of multivariate point processes is mandated by terminal heterogeneity. Subscript k or j represents, respectively, the cluster or component the point pertains to. The #j individual component point process is

$$\{p_{1,j}, \ldots, p_{k,j}, \ldots, p_{n,j}\}. \quad (6)$$

The statistical features of cluster point processes are essentially those summarized above for the bursty total spike trains of correlated convergent arrangements (Sects. 2.1 and 2.3) (Bryant et al. 1973). Their Fourier frequency representations involve spectra of counts (as far as we know, not of intervals) (Daley and Vere-Jones 1980). Expressions have terms that reflect either filtered versions of the spectrum of the burst series or the internal structure of the bursts, thus, respectively, the primary and subsidiary processes.

2.3 Total trains of correlated terminals as cluster point processes. Natural embodiments of process constituents

The notion that the point process representation of bursty total spike trains of correlated synchronous terminals are samples from cluster point processes is justified because of the oneness of the ways in which they are generated. Indeed, spikes form bursts and points form clusters in ways that conceptually are identical; the sum and substance of this shared conceptualization is that spikes and points from different sources arise at about the same instants and, being contemporary, group forming aggregates called, respectively, "spike bursts" or "point clusters".

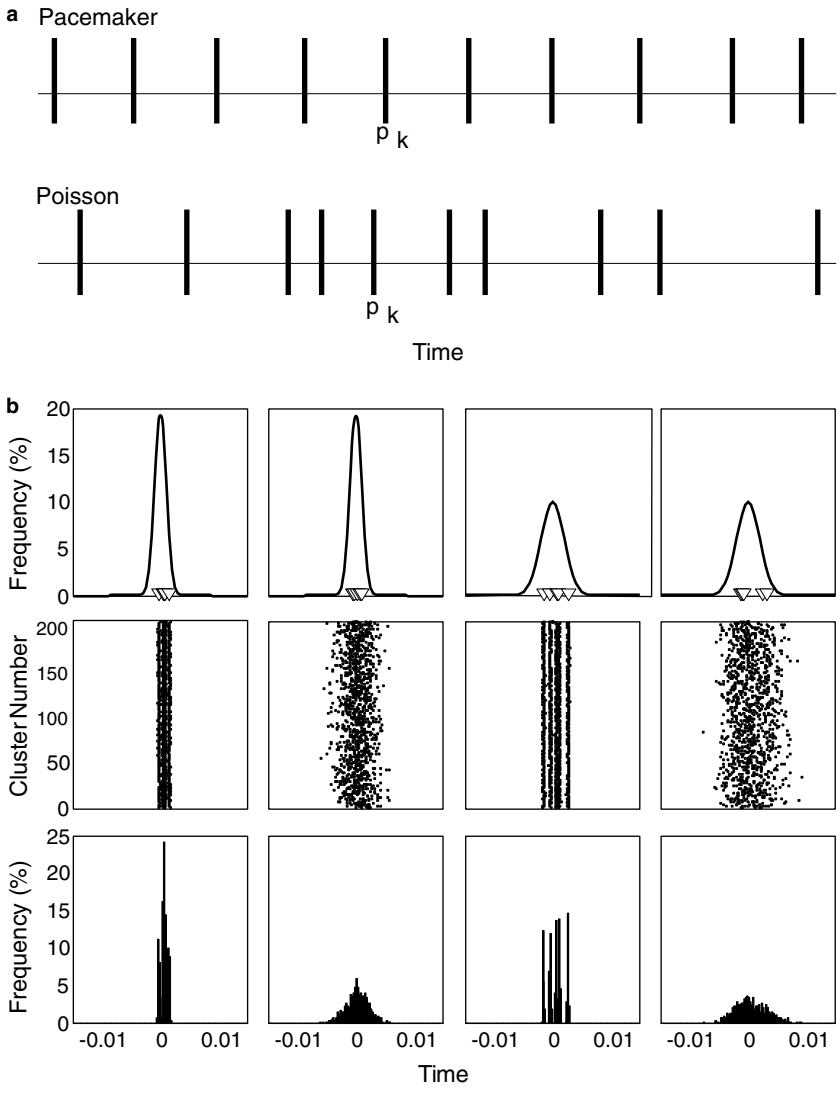

Fig. 3. **a** Primary process (α) specifying the timing of centers p_k: pacemaker (*top*), Poisson with short dead time (*bottom*). **b** Subsidiary process (β) specifying how points $p_{k,1}, \ldots, p_{k,j}, \ldots, p_{k,N}$ forming each cluster scatter around their center p_k; all clusters had $N = 10$ points. *Columns* imply different point dispersions around centers p_k; *points* correspond to separations $b_j + d_{k,j}$ obtained with different combinations of standard deviations in the Gaussian densities $\mathbf{\Phi}_1\{0, \sigma_1\}$ and $\mathbf{\Phi}_2\{0, \sigma_2\}$. *Top row*: Gaussian densities $\mathbf{\Phi}_1\{0, \sigma_1\}$ (expressed as percents) provide a single sample of N values bj (down-pointing *arrows below*) that, added to each center, give the "basic" clusters $p_k + bj$; all basic clusters involve points with identical separations from the respective center. Gaussian density $\mathbf{\Phi}_2\{0, \sigma_2\}$ (not drawn) provides n sets each with N values that shift all basic cluster points creating n "definitive" clusters $p_k + bj + d_{k,j}$; all definitive clusters in principle differ. *Central row*: Each *raster sweep* centered on the respective center p_k represents a particular definitive cluster showing how points separate from the respective center. *Bottom row*: Histograms (expressed as percents) estimating the density of point separations $b_j + d_{k,j}$ from their centers. Rasters and histograms correspond to individual clusters before pooling. From left, first column σ_1 small (0.001)-σ_2 small (0.0001); second small (0.001)-large (0.002); third large (0.002)-small (0.0001); fourth, large (0.002)-large (0.002)

As a consequence, the formal constituents of the process have obvious functional meanings and implications, thus natural embodiments. Each embodiment is independent of the others. Primary processes (α.), specifying center and cluster timings, reflect the recurrence in time of the referent events associated with the spike bursts in the convergent sets. Each referent event composes in time a series whose characteristic timings are many and heterogeneous (Sect. 2.1).

Subsidiary processes (β.), specifying point dispersion and number per cluster, reflect jointly events and circuits. Indeed, the referent event has a profile in time (magnitude, derivatives) that molds the final input to the target cell. Profiles, pulselike, quasisinusoidal vibrations, pattern generator output shapes, etc., are also many and heterogeneous: often, events (e.g., taps, clicks, twitches) with greater magnitudes and shorter durations associate with tighter, briefer bursts with more spikes. Also, molding the final input are the neural circuits interposed between events and convergent sets; circuits, too, involving different latencies, conductions, connectivities and operational time frames, can also be many and heterogeneous.

Poolings (γ.) join subsidiary processes in shaping individual clusters. Poolings stipulate, for example, keeping or ignoring component identities. Identities, obviously meaningful when terminals are involved, reflect the intrinsic anatomical and physiological details of the convergent arrangement; different identities reflect terminals with dissimilar sources and synaptic contacts, as well as different postsynaptic contributions to individual synapse.

Independent point processes and their poolings will be used in simulations as reference. Physiologically, independence is no less important than correlations, and both jointly embrace the formal background for total spike trains in converging synaptic arrangements. Studied extensively elsewhere, independence is not the main target of this communication and will be mentioned only briefly. It is well known that when poolings involve independent components in increasing numbers, the counts in an interval of given duration and the intervals between successive points asymptotically approach, respectively, Poisson and exponential distributions. In short, the pooled processes tend to the Poisson (Cox and Lewis 1966; Feller 1966). One of the mutually equivalent defining properties

of the stationary Poisson point process stipulates serially independent exponentially distributed intervals without a minimum. Feller (1966), who among others proved this asymptotic result, gave a qualitative version of the rationale stating that, roughly, the approximation takes place when the points from each component event become " ... extremely rare so that the cumulative effect is due to many small causes." The statistical Poisson-like properties of the superposition are "local," in the sense of holding only over periods of time that contain many events and point sets rarely including more than one point from each component, all of which therefore are individually sparse; approximations depend on the magnitudes of the mean individual and pooled intervals between points. Constraints are that components be in sufficient numbers and balanced (e.g., like averages) so that none dominates. Individual patterns can be any (e.g., "Poisson with dead time," "pacemaker" with all intervals close to their average, etc.), and all patterns need not be the same. Individual patterns affect the number of processes needed for pooled samples to approach a Poisson: obviously, just one suffices when its pattern is Poisson with a very short dead time, and several would be necessary if all were very periodic. These formal restrictions are not unduly restrictive physiologically: in pooled trains, the lack of interval minima does not clash with refractoriness.

3 Simulated experiments

Clearly, each physiological entity (terminal, spikes, trains, bursts) implies its formal counterpart (component, points, point processes, clusters), and vice versa (Sect. 2.2.2). Accordingly, the correlation-related issues tackled were translated into formal terms by substituting the physiological entities by the cluster point process constituents they embody. The simulated experiments were then designed within that formal context (Sect. 3.1.1). Experiments explored how primary processes affected postsynaptic intensity and dispersion (Sect. 4.1), how subsidiary processes and poolings affected the roles of presynaptic and postsynaptic spikes as predictees and predictors (Sect. 4.2.1), what happened when subsidiary processes enhanced or relaxed cluster synchrony (Sect. 4.2.2), how subsidiary processes and poolings influenced spatial summation of excitatory and inhibitory terminals (Sect. 4.2.3), and how biases impressed by other converging sets affected outcomes (Sect. 4.3). Finally, conclusions were translated back to the physiological domain for their final interpretation. Questions will be discussed in Sect. 5.2.

Section 5.2.5 shows values assigned to the variables in most simulations and are in the range reported for living neurons (e.g., Lux and Pollen 1966), but results do not depend qualitatively on them. Parametric analysis, though not exhaustive, sufficed to show that results happened within physiological domains and were reasonably robust: hence, the rules extracted from data may apply to living entities. Obviously, individual clusters and bursts could have arisen in series with many other timings (i.e., averages, patterns), and clusters had other structures (synchronies, numbers of spikes, components). Moreover, depending also on postsynaptic variables, each burst could have triggered several, one, or no spikes (resembling, respectively, climbing fibers, motoneurons, or invertebrate EPSPs, Fig. 1a-A, B).

3.1 Data generation

3.1.1 Preparations. Figure 1a-E illustrates that preparations included two presynaptic arrangements and one shared postsynaptic neuron. PSP amplitudes a were normalized to the difference between the postsynaptic potential and threshold asymptotes (see below); terminals were excitatory, except when otherwise indicated. The arrangement includes a moderate number of terminals N, usually 10, less frequently 20 than those in Fig. 1a-C. Terminals were called $\#1, \ldots, \#j, \ldots, \#N$, reflecting the order in which they tended to fire (see below). EPSPs, with $a \approx (\Delta/10)$, were called "small". The second group of afferents, similar to those in Fig. 1a-D, includes many terminals and "minute," almost negligible EPSPs ($N \to \infty$ and $a \to 0$, meaning huge and vanishingly small, respectively). Examples of both types of afferents are, respectively, Ia afferent or parallel fibers on dorsal spinocerebellar tract or Purkinje neurons, (e.g., Fujii et al. 1996; Henneman et al. 1974; Mendell and Henneman 1971; Salinas and Sejnowski 2000, 2002; Shadlen and Newsome 1995). Figure 1a-A involves powerful single terminals where one presynaptic spike triggers one or more postsynaptic ones ($N = 1$, $a \geq 1$); B involves moderately powerful terminals where at least, say, three spikes are needed to trigger [$N = 1$, $a \approx (\Delta/3)$]. Examples are climbing fiber-Purkinje and neuromuscular junctions in vertebrates or several synapses in mollusks, crustacea, or vertebrates, respectively.

The spontaneously silent postsynaptic neuron was represented by the well-known leaky integrate-and-fire (LIF) model (Fig. 1b) (e.g., Holden 1976). The membrane potential $P(t)$ evolved according to:

$$\frac{dP}{dt} = -\tau_P P + \sum I_i \,. \tag{7}$$

Presynaptic spikes elicited postsynaptic current pulses (I_i) of duration d_{syn} and amplitude I_{syn}; pulses determined EPSPs of amplitudes close to a (Table 1). τ_P is the membrane time constant. Excluding postsynaptic spiking, $P(t)$ evolved with the pooled Poisson arrivals of independent drives as shot-noise (Davenport and Root 1958) or with correlated drives according to the selected cluster point process (see below). $P(t)$ also reflected a bias B due to the minute EPSPs elicited by independent terminals (Segundo et al. 1968). Spikes occurred when $P(t)$ became equal to $H(t)$, i.e., when $H(t) - P(t) = \Delta_{PH}$ became 0. Reset after spikes were $P(t)$ to $P_\infty + B$ and $H(t)$ to $H(t) + H_d$, decaying exponentially with time constant τ_H. The variation of $H(t)$ represents the evolution of refractoriness. Time spans were judged long or short relative to τ_P, average rates low or high relative to $1/\tau_P$, and voltages large or small relative to $H_\infty - P_\infty$.

Following the classic work of Davenport and Root (1958), formal and experimental approaches to $P(t)$

Table 1. Model parameters

Variable name	Symbol	Value
Membrane potential initial value (mV)	$P(0)$	−60
Membrane potential asymptotic value (mV)	P_∞	−60
Membrane time constant (ms)	τ_P	10
Synaptic current duration (ms)	d_{syn}	0.1
Synaptic current amplitude (μA)	I_{syn}	1
EPSP amplitude (mV)	a	0.1
Bias (mV)	B	19–20
Threshold initial value (mV)	$H(0)$	−40
Threshold asymptotic value (mV)	H_∞	−40
Threshold time constant (ms)	τ_H	10
Threshold increment (mV)	H_d	10
Presynaptic terminal number	N	10
Primary process average interval (ms)	μ	10
Subsidiary process first standard deviation (ms)	σ_1	5
Subsidiary process second standard deviation (ms)	σ_2	0.4

fluctuations abound and, almost without exception, incorporate threshold parameters representing postsynaptic excitability (e.g.,Brunel and Sergi 1998; Burkitt 2001; Burkitt and Clark 2001; Calvin and Stevens 1968; Fourcaud and Brunel 2002; Feng and Zhang 2001; Gerstein and Mandelbrot 1964; Hohn and Burkitt 2001; Levitan et al. 1968; Salinas and Sejnowski 2000, 2002; Segundo et al. 1968; Shadlen and Newsome 1995; Svirskis and Rinzel 2000). Recently, Burkitt and collaborators (Burkitt 2001; Burkitt and Clark 2001; Hohn and Burkitt 2001) expanded LIF model uses, exploring rarely incorporated parameters (e.g., inhibitory reversal potentials) and noting novel consequences (e.g., how excitation to inhibition balances influence "dynamic ranges" and output dispersions). They judiciously insist that approximations (Gaussians, uncorrelated inputs, etc.), though inherent to models, require systematic parametric studies and matches with data from living preparations. Feng and Zhang (2001), besides other contributions, proved theoretically that consequences could be model dependent. For example, similar correlation shifts influence output variability and signal-to-noise ratios inversely in LIF and Hodgkin–Huxley models: the critical issue is the $P(t)$ decay rate, respectively, potential-independent or potential-dependent.

Brunel and Sergi (1998) examined the forcing by random Gaussian inputs of LIF neurons whose membrane time constants were frankly longer than those at the excitatory synapses, which, therefore, filtered the diffusion inputs with shorter time scales; their results, combining analytical and numerical procedures, give an expression for that neuron's firing rate, as a function of the synapse to membrane time constant ratio.

Fourcaud and Brunel (2002) contributed a detailed and exhaustive analytical description of a neuron's linear dynamical response to cosine inputs in the presence of noise. They used integrate-and-fire (simple or leaky), fixed-threshold models. Reasoning was within the framework of diffusion approximations and Fokker–Planck equation expansions. Neurons tend to fire irregularly but, provided appropriate constraints are met, exhibit average instantaneous rate and firing probabilities that map faithfully the oscillatory drive's profile in time, i.e., behave linearly. When the noise is white, the amplitudes decay with the reciprocal of the frequency's square root and lags approach 45° but, when noise is more realistic, amplitudes remain finite at high frequencies and limit phase lags disappear. The authors extend consideration to more biological conditions. No less desirable would be matching the linear domain (e.g., with large noise-to-signal amplitude ratios) with those of the nonlinear behaviors encountered with several drives in living and simulated preparations (e.g., Segundo 2003a,b; Segundo et al. 1998a,b).

3.1.2 Procedures. The preparation (Fig. 1a-E) included a weak terminal set eliciting small EPSPs: the jth terminal elicited a small EPSP of size a_j $(j = 1, \ldots, N)$, excitatory unless otherwise specified. Sizes, all close to an assigned value $(a > 0)$, differed little between terminals: a was such that, with $P(t) = P_\infty$ and $H(t) = H_\infty$, triggering occurred only if all terminals fired almost simultaneously $[(N-1)a < H_\infty - P_\infty < Na]$. Individual terminal average rates m_j and intervals T_j, because of conventions indicated below, were the same as values m and NT assigned to the primary process. Spike trains in all terminals had statistically similar patterns. In short, as is common in nature, no terminal differed markedly or predominated. Pooled average rates and intervals were Nm and $T = 1/Nm$.

The pooled presynaptic spike trains were samples from specified cluster point processes (Sect. 2.2.2), thus simulating total spike trains in sets of correlated synchronous terminals. Primary processes $(\alpha.)$, subsidiary processes $(\beta.)$, and poolings $(\gamma.)$ were such that they imposed the correlations involved in the questions selected. Reference inputs with independent terminals were samples from Poisson point processes or shuffled (described below).

Primary processes $(\alpha.)$ imposed the timing of the point process representing the series of n centers p_k $(k = 1, \ldots, n)$ [(6)] and thus of clusters (Fig. 3a). Manipulating them served to explore the physiological question (Sect. 2.1.2)

of how the timing of the referent events (sensory stimuli, etc.) that induce the bursts influence postsynaptic intensity and dispersion (Sect. 2.1). Because of the adopted conventions, their average rate m and interval T ($m = 1/T$) were the same as those in each of the N individual terminals. Simulations used primary process timings such that the intervals between centers were picked independently of populations with specified probability densities. Primary processes in cases called "correlated pacemaker" had regular and predictable patterns whose interval densities were Gaussians with low (under 0.05) coefficient of variation (CV) (Fig. 3a). Primary processes in "correlated Poisson" cases (Figs. 2b and 3a) had irregular and unpredictable patterns whose serially independent intervals came from exponential densities with large CVs [pertaining to the Neyman–Scott class of stationary Poisson cluster processes (Cox and Isham 1980)].

Subsidiary process (β.) specify for each cluster how many points it will have and how points separate from their centers p_k [(8), (9)]; implied are cluster profile and dispersion (synchrony) and cluster series consistency. Manipulating subsidiary processes explored the influences of the profile in time (magnitude, derivatives) of the referent event and their coding by the circuits between where events arise (e.g., sensorium, pattern generator output) and the converging terminals (Sect. 2.1.2). Stipulated first was that each component #1, . . . , #j, . . . , or #N, contributed a single point to each cluster, thus every cluster having N points, as many as components, i.e., each terminal fired once in every burst and there were as many spikes as terminals.

Subsidiary processes also stipulate the separation $s_{k,j}$ between each of the N cluster points $p_{k,j}$ and its center p_k; k and j represent, respectively, cluster and component. In simulations, separations were sums of independent Gaussian distributed variables b_j and $d_{k,j}$; hence, $s_{k,j} = b_j + d_{k,j}$. Both Gaussians (represented by $\mathbf{\Phi}$) had 0 means and different dispersions. The columns in Fig. 3b illustrates different subsidiary processes.

First specified was the Gaussian density $\mathbf{\Phi}_1\{0, \sigma_1\}$ (Fig. 3b-upper row). The same sample of N values from $\mathbf{\Phi}_1\{0, \sigma_1\}$ was assigned to all centers and clusters: it imposed upon all clusters the same basic structure. This "basic" sample (represented by arrowheads in Fig. 3b) was:

$$\{b_1, \ldots, b_j, \ldots, b_N\}. \tag{8}$$

j from 1 to N refers to their order in an increasing sequence ($b_1 < \cdots < b_j < \cdots < b_N$). k, identifying centers and clusters, is omitted because all shared the same values. This sample had average A_b and standard deviation S_1 close to, respectively, 0 and σ_1. The basic sample's N values were added to all n centers $\{p_k\}$ ($k = 1, \ldots, n$), creating n "basic" clusters:

$$\{p_k + b_1, \ldots, p_k + b_j, \ldots, p_k + b_N\}. \tag{9}$$

Points in all basic clusters were distributed identically around the respective center; as discussed below, the reason for this was to impose the tendency for components to appear (i.e., for terminals to fire) in the same sequence. Accordingly, subindices j reflect the order in which components tended to arise in clusters. This led to labeling the component (terminal) usually arising first . . . , jth,. . . , or last #1, . . . , #j, . . . , or #N. Basic clusters, though identically timed around centers p_k, surrounded different ones and happened at different times.

The second step specified another Gaussian density $\mathbf{\Phi}_2\{0, \sigma_2\}$ and took from it n independent samples of N values:

$$\{d_{k,1}, \ldots, d_{k,j}, \ldots, d_{k,N}\}. \tag{10}$$

The average A_2 and standard deviation S_2 of all n samples were close to stipulated values of, respectively, 0 and σ_2.

$\mathbf{\Phi}_2\{0, \sigma_2\}$ samples were used to convert each basic cluster into another cluster called "definitive." The kth basic cluster [(11)] was converted into the kth definitive cluster by taking each basic point $\{p_k + b_j\}(j = 1, \ldots, N)$, adding to it the value $\{d_{k,j}\}$ with its same j in the kth sample [(5)] and generating the jth definitive point $p_k + b_j + d_{k,j}$. Definitive points were random shifts of basic points. The kth definitive cluster, probably different from all others, follows:

$$\{p_k + b_1 + d_{k,1}, \ldots, p_k + b_j + d_{k,j}, \ldots, p_k + b_N + d_{k,N}\}. \tag{11}$$

Gaussians jointly shaped clusters, $\mathbf{\Phi}_1$ imposing a basic separation and sequence subsequently perturbed by $\mathbf{\Phi}_2$. Figure 3b, second row, displays rasters of several definitive clusters in isolation, i.e., before pooling; the bottom row shows the histograms of all $\{b_j + d_{k,j}\}$.

Finally, the n definitive clusters were pooled to produce a cluster point process with Nn points (N per cluster, n clusters). Cluster overlaps (allowed, see below) became less likely when the magnitudes of the primary process intervals between centers exceeded $(\sigma_1 + \sigma_2)$.

The average definitive separation was the sum of the average A_1 of the basic $\mathbf{\Phi}_1$ sample plus the average A_2 of the set of $\mathbf{\Phi}_2$ samples, thus $(A_1 + A_2)$ close to 0. Cluster dispersion, implying terminal synchronies, is measured appropriately by the variance $var(b_j + d_{k,j})$ over all clusters. It was the sum of the variance S_1^2 in the sample from $\mathbf{\Phi}_1$ plus the variance S_2^2 of the set from $\mathbf{\Phi}_2$, thus $(S_1^2 + S_2^2)$, close to $(\sigma_1^2 + \sigma_2^2)$.

When $\mathrm{var}(b_j + d_{k,j})$ was small (σ_1^2 and σ_2^2 small) (Fig. 3b, first column), clusters were tight; terminals were strongly synchronous and total spike trains clearly bursty. If $\mathrm{var}(b_j + d_{k,j})$ was 0 ($\sigma_1 = \sigma_2 = 0$), the timing of all components was that of the centers; terminals were absolutely synchronous. When $\mathrm{var}(b_j + d_{k,j})$ was large (σ_1 and/or σ_2 large) (Fig. 3b, fourth column), clusters lost individuality; terminal synchrony and bursting were weak. If very large, clusters overlapped, and terminal synchrony and bursting faded. σ_2 also controls cluster consistency; when small or large, clusters are homogeneous or heterogeneous, respectively.

Histograms of separations had preferred values at those of the shared sample (b_j) from Φ_1 (Fig. 3b, bottom row).

Points accumulated around modes according to Φ_2; multimodality faded when σ_2 increased (e.g., columns 3 and 4). The order $\#1, \ldots, \#N$ depends on the relation between σ_1 and σ_2. Its preservation becomes more likely when σ_1 exceeds σ_2.

Specifying when each terminal fires within bursts required preserving their identities and multivariate approaches: it thus related to *poolings* (γ.). Poolings served to explore questions such as whether terminal position along the cluster would affect what presynaptic and postsynaptic spike trains say about one another and what would happen when terminals were either excitatory or inhibitory.

The individual component processes and terminal spike trains were ($j = 1, \ldots, N$):

$$\{p_1 + b_j + d_{1,j}, \ldots, p_k + b_j + d_{k,j}, \ldots, p_n + b_j + d_{n,j}\}. \quad (12)$$

Rules excluded from clusters their centers and allowed cluster overlaps. Each component and terminal participated once in all clusters (see above); hence, individual average rates m_j and intervals T_j ($T_j = 1/m_j$) were the same as for primary processes, respectively, m and T. The instant when each point arose depended on the center it was attached to and on the separations imposed by the Gaussians, thus jointly on primary and subsidiary processes. Interval variances and standard deviations in individual components reflected those of the primary process and both Gaussians.

A few simulations involved IPSPs, in addition to the usual EPSPs. Both categories had the same PSP sizes (a and $-a$, respectively), averages, and numbers of terminals. Moreover, EPSP and IPSPs occurred in pairs: EPSP to IPSP delays δ were invariant. Negative or positive delays meant, respectively, IPSPs preceding or following EPSPs. Pairings implied that IPSP train timings were those of the EPSP partner [(12)] shifted by δ. The arrivals of both EPSPs and IPSPs during particular epochs are reported commonly in living nerve cells; consistent pairings are conceivable, though not yet looked for in data. Excitatory and inhibitory terminals converge upon, say, motoneurons from antagonistic muscles. The first correlations one thinks about are anticoincidences during limb movement but, because of complex interplays of tension, length and central controls; inhibitions as precise as the simulated pairings arise in time difference coding (Brand et al. 2002).

Obviously, any independent vs. correlated comparison of pooled processes should involve components with identical individual averages (Sect. 2.3). When simulating switches from independence to correlation averages do not vary, but patterns almost always do (Segundo et al. 1968). The unlikely risk of pattern, i.e., dispersion, sequence, interfering was reduced by first running the correlated case, taking one at a time the component processes $\#1, \#2, \ldots,$ or $\#N$, permuting their intervals, pooling the permuted components, and using these "shuffled" pooled processes as the matched independent. Original and shuffled partners have identical averages and dispersions but, most likely, lack the associations within individual spike trains and between separate ones of correlated cases: tests showed that shuffling did indeed eliminate them.

The preparation (Fig. 1a-E) included also a set with a huge number N' ($>> N$) of independent weak terminals generating minute EPSPs of amplitude a' ($<< a$). They were assumed to induce superposed DC-like biases B equal to $a'N'm'\tau_P$ (Segundo et al. 1968). B changes were attributed to varying numbers of active terminals and/or averages. Biases served to illustrate how other variables can condition the consequences of particular correlations (Sect. 4.3).

3.2 Data analysis

Intensity was evaluated by averages (rates, intervals), dispersion by interval coefficients of variation (CVs) and ISIHs, and second-order properties by ACHs. They served to analyze the influence of referent timings (Sect. 4.1), burst synchrony extremes (Sect. 4.2.2), delays and order (Sect. 4.2.3), and conditionings by biases (Sect. 4.3). CCHs evaluated associations between spike trains in terminals (e.g., "presynaptic #1, presynaptic #10") or between the postsynaptic neuron and the individual terminal ("postsynaptic, presynaptic #j CCH"). The converse "presynaptic #j, postsynaptic CCH" used reference #j and estimated postsynaptically. The bin widths in the figures acceptably displayed the rate fluctuations judged relevant. CCH confidence bands were based on heuristic criteria. One was that peaks or troughs exceed the range of values at long delays when presumably all correlating influences had subsided. Others, adapted to specific questions, were that they appear at the same delays in all comparable histograms (e.g., all #j), or that values consistently exceed their neighbors every fixed number of bins.

4 Results

Figures 2 and 4 illustrate raw data. Figure 2 displays corresponding spike train rasters. With independent drives (a, c), individual presynaptic spike trains (presynaptic, $\#1, \ldots, \#10$) were either Poisson or shuffled (Sect. 3.1.2). Rasters suggest no tendencies of terminals to fire synchronously or in particular orders. Statistically, total or pooled spike trains (pool), irregular and unpredictable, were sampled from Poisson processes without dead times. With correlated Poisson (b), individual presynaptic trains reflected the chosen cluster point process. Separate terminals synchronized, usually firing in the $\#1, \ldots, \#10$ order. Pooled spike trains showed bursts that, because of the Poisson primary process, arose unpredictably. Most bursts triggered postsynaptic spikes (postsynaptic, at arrowhead tips); vertical dashed lines illustrate their relation with the presynaptic trains.

Figure 4 displays the postsynaptic $P(t)$ (thick line) and $H(t)$ (thin line); upwards $P(t)$ or $H(t)$ steps indicate, respectively, when EPSPs (presynaptic spikes) or postsynaptic spikes happen. Biases (attributed to a separate set with many independent terminals generating minute EPSPs) are "weak" (upper row), "medium" (center), or "strong" (lower). $P(t)$ fluctuations with independent

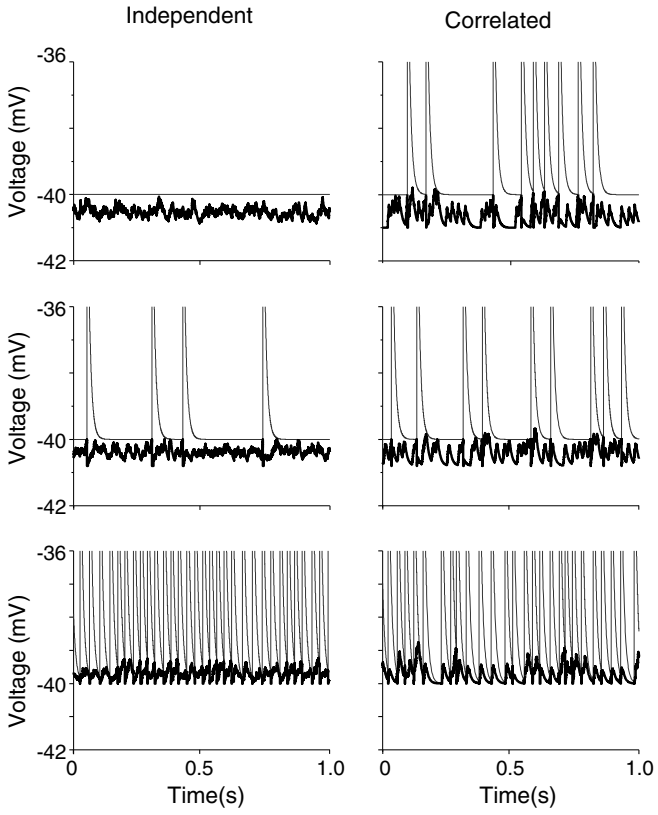

Fig. 4. Postsynaptic state variables. Membrane potential $P(t)$ (*thick line*) and threshold $H(t)$ (*thin line*). Steplike EPSPs are produced by presynaptic spikes. Bias: 19 mV (*upper row*), 19.2 mV (*center*), and 20 mV (*lower*). Independent drives (*left column*). $P(t)$ follows shot-noise, undistorted when there are no firings (*upper left*) or distorted by spikes elsewhere. Poisson correlated drives (*right column*). $P(t)$ fluctuations reflect the cluster point process

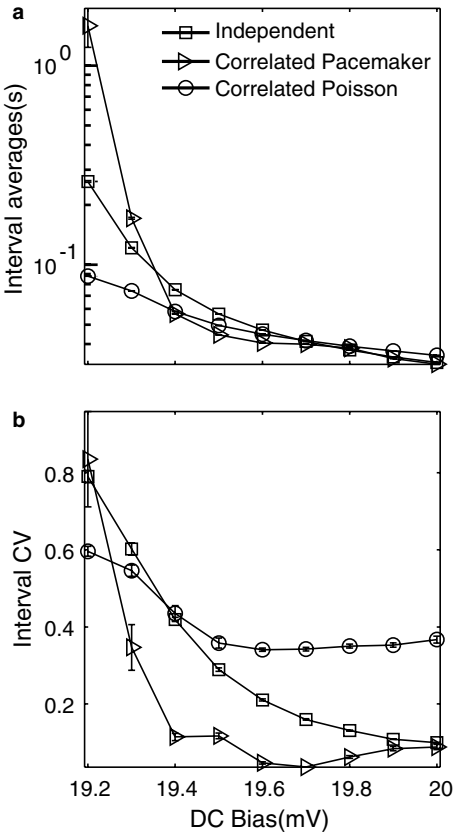

Fig. 5. Conditioning by bias. **a** Postsynaptic interval average (semi-logarithmic plot). **b** Coefficient of variation. *Abscissae*: Bias relative to the potential asymptote P_∞. Symbols (each from a sample with 20 simulations of up to 20 s duration or with up to 500 output spikes): *circles* – correlated Poisson, *triangles* – correlated pacemaker, *squares* – independent. *Vertical bars*: Standard deviation of each estimate in the sample (some are small and contained in the *circles, squares* or *triangles*)

drives (left) evolved as shot-noise distorted by postsynaptic spikes and resettings; with correlated drives (right), $P(t)$ fluctuated according to the cluster point process, correlated Poisson.

An expected key finding was that $P(t)$ reached the $H(t)$ level and triggered at special waveforms imposed by special pooled timings (Segundo et al. 1966). Triggering waveforms had globally overall positive-going displacements, steep slopes, and large amplitudes; triggering timings involved successively shorter intervals (accelerating) with a short average (high average rate). This is apparent in Figs. 2 and 4. The timing of the series of triggering events (waveforms, pooled sets) determined that of the postsynaptic discharge: both were identical when each event triggered one spike. Triggerings with independent terminals occurred unpredictably; with correlated terminals, they occurred at instants stipulated by the Poisson (Figs. 2b and 4) or pacemaker primary processes.

Figure 4 also suggests results in Sects. 4.1 and 4.3. With weaker (upper row) or stronger (lower) biases, firings were, respectively, slower and irregular or faster and regular. With weaker biases (upper) there were more triggerings with correlated (right) than with independent (left) drives; with stronger biases (lower), both were about as effective.

4.1 Primary processes. Postsynaptic intensity and dispersion

Figure 5 shows that dissimilar primary processes associate with outcomes conditioned by the superposed biases (on abscissa) (Sect. 4.3). Throughout Fig. 5 the intrinsic structures of the individual clusters, and thus the synchronous presynaptic bursts, though differing in precise details, are statistically identical. Each mark comes from a sample based on 20 simulations, each lasting up to 20 s or with up to 500 output spikes; vertical bars represent the standard deviations of the estimates in the corresponding sample. Figure 5a with a logarithmic ordinate displays the postsynaptic interval averages that evaluate intensities. At the weakest biases, the influence of the primary process controlling cluster and burst timings is clear. Correlated Poisson (circles) imposed the shortest intervals (highest rates). Contrastingly, correlated pacemaker (triangles) practically did not trigger, their extremely long averages requiring logarithmic ordinates. This reflected that at weak biases the standardized cluster or burst triggered when, as in the correlated Poisson, the intervals between it and other such bursts occasionally were short

enough to allow successive ones to add their contributions; the same bursts triggered rarely or not at all when, as in the correlated pacemaker, they systematically occurred far from other bursts. As expected, when biases increased, average intervals decreased, reaching a plateau (saturating); dissimilar drives differed less, eventually becoming indistinguishable from one another. The primary process average of 0.010 s separated correlated pacemaker clusters and bursts, and about one every four triggered. These contrasts involving biases and Poisson versus pacemaker patterns match those at different $P(t)$ levels in *Aplysia* neurons driven by moderate EPSPs (Levitan et al. 1968).

Figure 5b displays postsynaptic interval CVs evaluating dispersion or variability. With a correlated Poisson (circles), CVs at all biases were relatively high, never under 0.3 and around 0.60 at weak ones. With a correlated pacemaker (triangles), CVs at all biases were low, never over 0.20 and at strong ones around 0.10; ISIHs and ACHs (not shown) confirmed and extended this. Clearly, then, the regularity of how bursts arise has postsynaptic consequences, and changing it may increase or decrease output dispersion.

Independent drives (squares) behaved differently (Segundo et al. 1968). At weak biases, they elicited few spikes at long interval averages (low rates); CVs were the highest (around 0.8). At strong biases, averages (around 0.03) were the smallest (highest rates) and CVs (0.10) low.

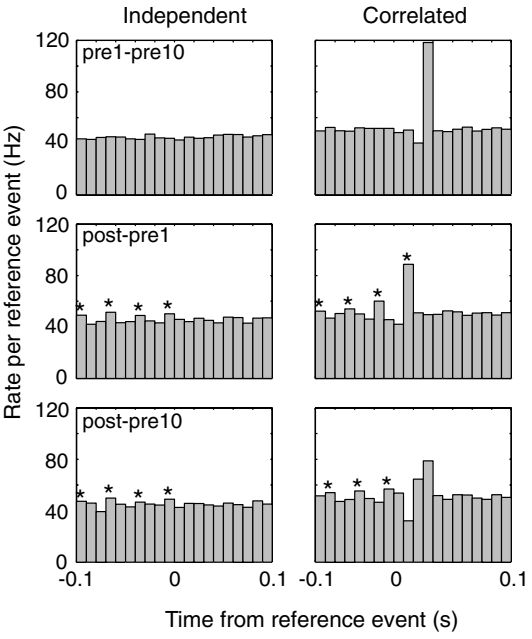

Fig. 6. Crosscorrelation histograms (CCHs). On *abscissae*, time from reference spike; on *ordinate*, average number of the other spikes in each bin, normalized to per-second and per-reference event. *Asterisks*: Peaks reset by presynaptic spikes indicate the presence of postsynaptic periodicities. Large bias (19.8 mV). Drives: independent (*left column*); correlated Poisson (*right*). *Upper row*: "Presynaptic cell #1, presynaptic cell #10" CCH. *Center row*: "Postsynaptic cell, presynaptic cell #1" CCH. *Bottom row*: "Postsynaptic, presynaptic cell #10"

4.2 Subsidiary processes and poolings

4.2.1 Crosscorrelation histograms. Subsidiary processes stipulate timings and numbers of points within clusters and bursts; poolings stipulate superposition rules, such as preserving component and terminal identities and thus revealing tendencies to particular sequences. Jointly, they impose burst structures and consistency along the series.

CCHs, evaluating time domain associations between postsynaptic and presynaptic spike trains, had the characteristic features assigned to excitatory synapses (Bryant et al. 1973), namely, features due to synaptic influences, presynaptic periodicities, postsynaptic periodicities, and correlated events. All tended to be more obvious with correlated than independent drives.

Figure 6 (strong biases) displays matched CCHs. Independent drives (left column) had flat CCHs between all presynaptic pairs (e.g., "presynaptic #1, presynaptic #10," upper row). Moreover, all "postsynaptic, presynaptic #j" CCHs were practically the same. "Postsynaptic, presynaptic #1" (center), say, shows a small central peak to the left of the origin. This means that reference postsynaptic spikes tended to be preceded within the bin width (10 ms) by mild accelerations in #1. In the converse CCH (not shown) with presynaptic references, this peak would be to the origin's right, and, equivalently, spikes in individual terminals tended to be followed by mild postsynaptic accelerations. This peak was judged significant, even if differing little from values encountered at long delays, because it appeared in all ten comparable CCHs (using {#1, . . . , or #10}). Under the null hypothesis that the bin did not differ from its neighbors, one can argue nonparametrically that on the basis of chance alone the encountered excesses could happen around once in 1024 (2^{10}) cases. Peak smallness reflects that each terminal had a weak effect and that, as others, it triggered only about one every ten postsynaptic spikes.

Independent cases showed also other CCH peaks, particularly with strong biases. They occurred periodically, approximately every 30 ms (i.e., every three bins); present on both sides of the origin, they were clearer to the left (asterisks). Present in all CCHs, under the null hypothesis that bin values in every third bin to the left of the origin did not differ from their neighbors, their presence in all #1– #10 CCHs could happen very rarely on the basis of chance alone. (Periodicity manipulations described below supported this significance). Thus, time-locked to the postsynaptic spike, particularly prior to it, terminal #1 (or any other) tended to fire periodically. Equivalently, time-locked to a presynaptic spike and particularly following it, the postsynaptic neuron fired periodically. That period, or related ones, was absent or not outstanding presynaptically: trains were either pacemaker with unrelated periods or aperiodic Poisson. Moreover, when the postsynaptic τ_H was changed from 10 ms to 20 ms, this periodicity switched to around every 70 ms; likewise, it disappeared when τ_H was 1 ms. Thus, this periodicity arose postsynaptically. Prevalence to the left of the origin here (or to its right in the converse CCH) implies that presynaptic spikes reset it (as happens in a tuning fork when struck).

In correlated drives, "presynaptic #1, presynaptic #10" CCH (upper row, right column) presents a clear central trough-peak complex to the origin's right: hence #1 spikes

were followed almost immediately by #10 slowings but, after around 10 ms, by accelerations. This reflected the fact that, following the early terminal's spike at the beginning of the burst, the likelihood of late spikes firing was low immediately but became high at its end. Central peaks and troughs are considered statistically significant because they exceed CCH fluctuations far from the origin, when presumably correlation-inducing issues had faded: this contrast is sufficiently clear to the naked eye to make bars unnecessary. If individual terminals fired several consistently timed spikes per burst (instead of one as was usual), central peaks were multimodal.

The "postsynaptic, presynaptic #1" CCHs of correlated drives (right column, central and bottom rows, correlated Poisson) confirmed that, in addition to the (weak) consequences of the plotted terminal, they reveal the influence of others firing almost simultaneously (Bryant et al. 1973). Moreover, postsynaptic spikes usually were triggered close to a burst's midpoint, thus following early, being around intermediate and preceding late presynaptic spikes (e.g., #1, 5 and 10). Accordingly, in the corresponding "postsynaptic, presynaptic #j" CCHs, the delay relative to the postsynaptic spike reference revealed the terminal's favored position in the cluster. The "postsynaptic, presynaptic #1" CCH (center) showed central effects just to the left of the origin, meaning that the postsynaptic spike tended to be preceded immediately by more #1 spikes than average (accelerations) preceded in turn by fewer (slowings); equivalently, #1's spike tended to be followed first by a postsynaptic acceleration and then a slowing. The "postsynaptic, presynaptic #10" CCH (bottom) showed the central complex more to the right, the trough barely preceding the reference and the peak following it: postsynaptic spikes were preceded by #10 slowings) and followed by accelerations. Equivalently, #10's spikes were followed by postsynaptic slowings and preceded by accelerations.

Other "postsynaptic, presynaptic #j" CCH peaks and troughs could exist away from the origin, reflecting the timing of the burst series as well as their structure and consistency, thus all process constituents. They were most noticeable in correlated pacemaker cases (not shown) when bursts arose periodically, closely resembling central ones, particularly with narrow and consistent bursts. They were practically absent in correlated Poisson (Fig. 6), when bursts were aperiodic, particularly if also broad and heterogeneous. Finally, smaller peaks (asterisks) reflecting postsynaptic periodicities were also present, exhibiting the same periods as with independent drives.

4.2.2 Cluster synchrony. As synchrony increased within the set of weak terminals (Fig. 3b, from fourth to first, ignoring second column), the consequences of each burst approached those of the single spike in a powerful terminal; this will be described extensively elsewhere (Gómez et al., unpublished manuscript). In the first place, the central features in all "postsynaptic, presynaptic #j" CCHs were emphasized; moreover, all CCHs approached those of early terminals, becoming more similar and independent of #j. Emphasized also were the features revealing postsynaptic periodicities. With extremely small variances, CCHs resembled those at single powerful synapses (Fig. 1a-A, B). In fact, when the tight bursts had different timings (i.e., reflected different primary processes), the postsynaptic spike trains exhibited forms that closely resembled those imposed by powerful terminals and proven to embody universal periodic, quasiperiodic, aperiodic behaviors (Segundo et al. 1998a). (A "form" is a category of timings defined by shared specified properties). This important aspect will be covered by Gómez et al. (unpublished manuscript). Increasing subsidiary process variances stretched individual clusters, weakening synchrony and consistency: "postsynaptic, presynaptic #j" CCH features attenuated.

4.2.3 Spatial summation of convergent excitatory and inhibitory terminals. Noncommutativity. Some simulations included paired EPSP and IPSPs separated by delays δ. Figure 7 illustrates how delays (abscissae) affected output average intervals (ordinates). Panels correspond to different subsidiary process variances; all were correlated Poisson cases with the same values used in Fig. 3. In all panels, the longest output average intervals (lowest rates) occurred with delays close to 0, indicating that IPSPs thwart triggerings more efficiently when close to EPSPs. Moreover, plots were asymmetric, showing greater lengthenings when IPSPs led EPSPs (negative delays) than when they lagged (positive delays). Only when the clusters were tight and inconsistent did the largest interval correspond to zero delay. Lengthenings were more marked with dispersed, consistent clusters (bottom left) than with tight variable ones (upper row).

4.3 Conditioning by biases. Heterogeneous results

Biases were attributed to numerous independent weak terminals eliciting minute EPSPs. Figure 5 summarizes how biases conditioned the consequences of each drive. Maximally influential biases (at least from 19 mV to the maximum tested 20 mV) put $P(t)$ close to $H(t)$.

As biases increased, predictably the average postsynaptic intervals (a) of all drives first decreased (rates increased) monotonically and, when biased potentials were slightly less than H_∞ (around 19.5 mV), all reached similar minima; further depolarizations caused no further changes (saturations). CV changes with increasing biases (b), on the other hand, were drive dependent. With a correlated Poisson (circles), CVs at the weaker biases were large and fluctuated (around 0.60), decreased to a local minimum, subsequently increasing to reach another maximum and finally decreasing to an overall minimum (not shown). What underlies this was not examined.

With correlated pacemaker (triangles), CVs were large (around 0.8) at the weakest biases when postsynaptic firing was sparse. When biases were strengthened, the CVs decreased rapidly to small values (under 0.1) and remained so throughout. The plot was not monotonic, and the smallest CVs close to 0 occurred at intermediate biases. Identifying the reason for this, which would have required extensive

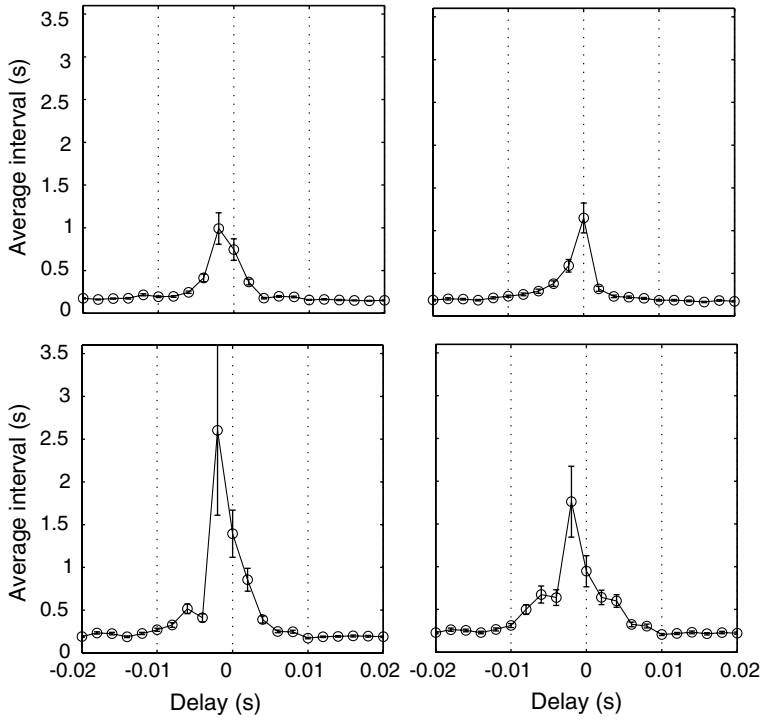

Fig. 7. Converging excitatory and inhibitory terminals. Separation and sequence. Noncommutative summation. Average postsynaptic interval (*ordinates*) as function of delay from EPSPs to IPSPs (*abscissae*): negative (IPSPs preceding EPSPs), positive (IPSPs following EPSPs), 0 coincidence. Biases were the same for all entries. Each *point* corresponds to one simulation; *bars* correspond to the standard error. *Panels* correspond to involved subsidiary processes used in different columns of Fig. 3b: *top left*: first column; *top right*: second column; *bottom left*: third column; *bottom right*: fourth column

formal and simulated efforts, was not examined. With independent drives (squares), CVs as reported (Segundo et al. 1968) at weak biases were large (around 0.80), but, as biases augmented, they decreased monotonically, achieving around 19.5 mV small values (under 0.20) and maintaining them beyond. Concomitantly, ISIHs narrowed, ACHs became more periodic with higher peaks and 0-valued troughs. Thus, output patterns tended to pacemaker.

Biases affected the relative CV magnitudes: these, listed in order of decreasing value, were "independent, correlated Poisson, correlated pacemaker" at weak biases but "correlated Poisson, independent and correlated pacemaker" at strong biases.

Each finding occurred within a domain circumscribed by variables involving correlations and other issues (Sect. 3). The restricted parametric analyses performed, though not exhaustive, sufficed to prove that variables were influential within physiologically meaningful domains.

5 Discussion

5.1 The thesis

Our thesis contends that, if presynaptic terminals in convergent arrangements correlate, the pooled spike train composed by superposing all individual trains is the realization of a cluster point process (Sect. 2.1). The rationale simply is that conceptually the two entities are identical. This interpretation of pooled correlated spike trains joins the well-known proposal that those of independent cases are realizations of Poisson point processes; between them, therefore, they complete the formal approach to the pervasive and functionally important convergent arrangements.

Furthermore, as discussed below, their primary process, subsidiary process, and pooling constituents have, not only separate independent formal roles, but also separate independent physiological embodiments (sensory, motor, synaptic, etc.) (Sect. 2.2). Embodiments are many and heterogeneous (Sects. 2.1 and 2.3) and thus so are physiologically plausible constituents, which can impose series anywhere from regular predictable to irregular unpredictable, synchronies from barely demonstrable to extreme, structures from simple to complicated, and consistencies from slack to faultless. Recent work extends the domain of correlated firing implications to the peripheral and central neural development (e.g., Buffelli et al. 2004).

The above allows for innumerable plausible fluctuations in correlations, supporting the idea that convergent sets contribute within broad and diverse physiological domains to neural, including synaptic, codings (see also Sect. 5.2.2) (Segundo et al. 1994). In fact, proof abounds that all cluster point process constituents and their embodiments participate widely in all such codings (e.g., Sects. 2.1 and 2.3) (Segundo et al. 1968, 1995; Segundo 2003a). Simulations confirmed this and added examples, and in so doing, they illustrate how that thesis can orient physiologically relevant research.

This formal proposal provides sensible guidelines for recognizing further physiologically meaningful questions and for providing suitable rules and criteria applicable to experimental designs and data interpretations. For example, using notions from nonlinear dynamics, it suggests strategies that involve taking an output characteristically driven by specific inputs as references and then exploring if and how that output persists when conditions are perturbed. Sections 5.2.1, 5.2.3, and 5.2.4 will illustrate more precisely why, conceivably, references and perturbations can involve, say, pacemaker series of bursts and their

irregularization, or perfect burst synchronies and their weakenings, or coincident excitation and inhibition and increasing leads or lags. Natural domains contain substantial portions wherein such tests have clear physiological meanings.

Cluster point processes may have been used, perhaps inadvertently, to represent the total input from correlated terminals. Indeed, several pooled correlated spike trains seem to comply with the definition of cluster point processes. For example, in Segundo et al. (1968), "source" neurons forced presynaptic terminals into synchrony, and, therefore, source spike train timings embodied primary processes; moreover, each source spike influenced the terminals with particular delays, firing probabilities, etc. that embodied subsidiary processes and poolings. In Salinas and Sejnowski (2000), all terminals shared the same fraction of the samples contributing to the postsynaptic spike triggerings; because of this, drives imposed similar (or proportionate) influences upon all terminals that, therefore, correlated. Hence, the timing of any presynaptic terminal could embody the primary process: the latter (close to either steady-state Poisson with short dead time or modulated periodically) could be deduced probabilistically from the specified variables; furthermore, the CCH between the terminal embodying the primary process and any other terminal would embody subsidiary processes and poolings.

The following sections (Sects. 5.2.1–5.2.5) will concentrate on findings judged novel and on how they depend on selected constituents with physiological connotations. Even though the constituents of the cluster point process are separate and independent, most output spike train features depend jointly on several of them.

5.2 Simulation outcomes

Simulations performed for this paper included only certain realizations of cluster point processes. For example, the probability of each component participating and each terminal firing in each cluster was always 1. Obviously, when this probability is close to 1, results are expected to be similar. It would be interesting to extend this study to the more general and biologically meaningful case of much smaller probabilities.

5.2.1 Postsynaptic dispersion increases or decreases. The presynaptic frequency composition imposed by the cluster point process clearly marks the postsynaptic spike train; this was revealed by CVs, ACHs, "postsynaptic, presynaptic #j" CCHs, and other statistics.

Such frequency transfers, given their reported complexity when a single stronger terminal is involved, very likely require considerable separate projects (e.g., Segundo et al. 1998a): apparent in the present series were hints of nontrivial issues (e.g., results in Fig. 5 or commented in the next paragraph and Sect. 5.2.5)

Primary processes were major contributors, setting the timings (i.e., averages, patterns) of the cluster series, the presynaptic pooled burst series, and the individual spike trains (Sect. 2.1). When, as in correlated pacemaker cases, primary processes involved strong low-frequency (long period) components (in nature often pacemaker) revealed by clear and repeated broad peaks, postsynaptic trains showed similar components (Fig. 5b-triangles) (Sect. 5.2.3). Contrastingly, the largely aperiodic primary processes of the correlated Poisson determined, unless biases were strong, postsynaptic spike trains without prevalent periodicities and with large CVs (circles). Shorter-period, higher-frequency periodicities, revealed by, for example, jagged broad ACH and CCH peaks, depended more on the intrinsic burst structures imposed by subsidiary processes and poolings.

This influence of the frequency composition of the series of bursts upon its postsynaptic counterpart had been reported earlier for steady-state and modulated drives (Sect. 4.1) (Brunel and Sergi 1998; Burkitt 2001; Salinas and Sejnowski 2000; Segundo et al. 1968). However, the broad spectrum of postsynaptic variabilities associated with correlations, as well as the fact that correlation shifts could just as well induce decreased as increased variabilities, has been somewhat overlooked. This may be because many earlier reports concentrated on largely irregular and unpredictable pooled spike trains, separating from Poisson processes only by excesses of the shortest intervals (e.g., Salinas and Sejnowski 2000, 2002; Svirskis and Rinzel 2000); thus excluded were the no less pervasive and vital situations with strongly periodic bursts. Earlier reports, even if contributory, have been insufficient in this respect.

5.2.2 Postsynaptic spikes as predictees and predictors (anticipators) of presynaptic spikes. It is valid to ask how much does the postsynaptic spike train say about the individual presynaptic spike trains and vice versa. Statistics of choice for answering this were the "postsynaptic, presynaptic #j" CCHs (Fig. 6-middle, bottom rows) and their converses "presynaptic #j, postsynaptic."

Postsynaptic spikes were triggered usually during presynaptic bursts and close to their middle; moreover, spikes in individual presynaptic terminals arose along bursts in the prevalent order #1, ... , #j, ... , or #N. As a consequence, the fact of a postsynaptic spike justified both inferring backwards in time when early terminals had fired and predicting forwards, i.e., anticipating, forthcoming firings in late terminals (e.g., respectively, #1 and #10, Figure 6, right column, middle and bottom rows). Anticipation implies simply that the individual convergent terminal's synapse does not pertain to the formal category of "causal" or "realizable" systems (Brillinger 1975); the just detailed rationale indicates clearly how, though in a roundabout way, causality is respected.

All CCH features became more conspicuous when passing from independent to correlated cases, as well as when burst synchronies increased (Sect. 5.2.3); these enhancements illustrate how CCHs at the particular synapse "presynaptic #j on postsynaptic neuron" reveal associations with events that, such as "spikes in other terminals," arise close in time with one of the paired spikes (Bryant et al. 1973).

The subsidiary processes and poolings were major contributors to the above. Subsidiary processes set point dispersions and numbers within clusters. They were embodied by referent event profiles in time and by how these profiles were transformed by the neural circuits interposed between events and convergent sets. Poolings further shaped individual clusters by, say, requiring that component's identities to be preserved; they thus were embodied by the anatomical and functional individuality of terminals and their synapses. Both contributed to cluster consistency.

5.2.3 Burst synchrony. Subsidiary processes control synchrony. At one extreme, barely synchronous (or independent) terminals impose a noisy background that can significantly condition other inputs to the same neuron (Segundo et al. 1994). At the other extreme, bursts of strongly synchronous terminals act very much like single spikes in more powerful terminals, mimicking the PSPs from climbing fibers, motoneurons, or invertebrate synapses (Fig. 1a-C, D mimic A, B) (Sect. 4.3). Relevant here is the point raised by Segundo et al. (1994) that, when influenced by conditions such as noisy sinelike skin indentations, convergent terminals can simultaneously be independent at high firing frequencies and synchronous at low frequencies, thus simultaneously providing noise and signal.

Accordingly, as synchrony increases, bursts tend to act like spikes in powerful terminals. Indeed, as will be reported extensively elsewhere (Gómez et al., unpublished manuscript), the pacemaker or Poisson correlated drives tend to impose output spike trains similar to those reported for stronger synapses driven by pacemaker or Poisson trains, respectively (Segundo 2003a,b; Segundo et al. 1998a,b). These outputs exhibit input-pattern- and average-dependent forms called "locked," "intermittent," "phase walk-throughs," "erratic," "stammerings," and "noisy." Segundo et al. (1998a) showed that forms embody the universal behaviors known as periodic, quasiperiodic or chaotic, noisy, intermittent, and windowings (skippings), also conjecturing they are building blocks for any synaptic coding. There would be great interest in extending analyses such as that of linear domains of combined signals and noise by Fourcaud and Brunel (2002) and Brunel et al. (2001) to these eminently nonlinear behaviors.

5.2.4 Delays, order, and noncommutative synaptic summation when excitation and inhibition coexist. The postsynaptic consequences of single bursts jointly reflect those of the individual terminals plus possible interactions. They are much more easily predictable when all terminals are excitatory and do not interact (as here and in several publications) than when terminals differ and/or interact (e.g., excitatory or inhibitory, facilitating or depressing, etc.).

Subsidiary processes and poolings are the major contributors, setting within burst timings and preserving the identity of the terminal that each spike pertains to. These details, implying interterminal delays and orders, are critical for interactions, whose significance is enhanced when terminals have dissimilar sources and/or postsynaptic consequences.

In our experiments, when convergent arrangements included both excitatory and inhibitory terminals (Sect. 4.2.3), output intensity and dispersion depended on the delays between the respective spikes (Fig. 7). Postsynaptic dispersions, for example, were largest with negative delays close to 0. The influence of order implied that spatial synaptic summation can be noncommutative. Dudel and Kuffler (1961) and Segundo et al. (1963) had found in crayfish and *Aplysia* order-dependent EPSP and/or IPSP summations, attributing these to asymmetric synaptic localizations and/or chemical processes. Hence, synaptic coding evaluations must take ordering into account, together with the usual statistics.

The influential delays were in milliseconds. This order of magnitude is far from unphysiological, for numerous publications have proven that in, say, mammals and birds, neurons are sensitive to differences in the millisecond and even the microsecond ranges (e.g., Brand et al. 2002; Moiseff and Konishi 1981; Moortgat et al. 1998); such results are compatible with the numerous psychophysical observations involving perception and behavior.

5.2.5 Conditioning by biases. Output heterogeneity. The numerous postsynaptic consequences of presynaptic correlations reflect first the number and variety of physiologically plausible cluster point processes. They reflect also that individual outcomes are conditioned by several variables, not necessarily participating in the correlations themselves. Present simulations (Sect. 3) included parametric analyses that, though limited, showed that each variable explored was influential within a multidimension physiologically meaningful domain. This was illustrated using biases as conditioning variable and evaluating average intervals and CVs (Fig. 5); biases were assigned to a separate set with many weak independent terminals eliciting minute EPSPs (Fig. 1a-E) (Segundo et al. 1968). Biases also conditioned the best strategies needed for "desired" outcomes. For example, correlated Poisson maximized postsynaptic intensity at weak biases, but all conditions were about equivalent at strong biases; independent terminals maximized dispersion at weak biases but correlated Poisson did so at strong ones; finally, correlated pacemaker (when triggering) minimized dispersion at all biases.

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