Either spontaneously or in response to stimuli, neurons are active in a coordinated fashion. For example, an onset response to sensory stimuli usually evokes a 50–200 ms long burst of population activity. In this chapter, we summarize recent papers of the author showing that such bursts of neuronal activity are not randomly organized, but rather composed of stereotypical sequential spiking patterns. To underline this fine-scale internal organization of such population bursts, we will refer to them as “packets.” It has been shown that packets are ubiquitous feature of spontaneous and stimulus-evoked network activity and are present across different brain states. Although these packets have a generally conserved sequential spiking structure, the exact timing and number of spikes fired by each neuron within a packet can be modified depending on the stimuli. In this chapter, we provide a detailed description of packets, and we discuss how the packet-like organization of neuronal activity may provide an explanation for multiple puzzling observations about neuronal coding. It is interesting to note that organizing population activity into packets resembles how engineers designed information transfer over Internet, where information is divided in small, formatted network packets to increase communication efficiency and reliability.

**Keywords**
Auditory cortex - Somatosensory cortex - Population coding - Temporal coding - Upstate - Slow wave oscillation - Silicon microelectrodes - Brain state - Memory replay
Chapter 8
Packets of Sequential Neural Activity in Sensory Cortex

Artur Luczak

Abstract Either spontaneously or in response to stimuli, neurons are active in a coordinated fashion. For example, an onset response to sensory stimuli usually evokes a 50–200 ms long burst of population activity. In this chapter, we summarize recent papers of the author showing that such bursts of neuronal activity are not randomly organized, but rather composed of stereotypical sequential spiking patterns. To underline this fine-scale internal organization of such population bursts, we will refer to them as “packets.” It has been shown that packets are ubiquitous feature of spontaneous and stimulus-evoked network activity and are present across different brain states. Although these packets have a generally conserved sequential spiking structure, the exact timing and number of spikes fired by each neuron within a packet can be modified depending on the stimuli. In this chapter, we provide a detailed description of packets, and we discuss how the packet-like organization of neuronal activity may provide an explanation for multiple puzzling observations about neuronal coding. It is interesting to note that organizing population activity into packets resembles how engineers designed information transfer over Internet, where information is divided in small, formatted network packets to increase communication efficiency and reliability.

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Introduction

Progress in recording from a large number of neurons [1–3] allowed to advance our knowledge on how the activity of a single neuron is shaped by the action of other neurons [4, 5]. It has been found that even in the absence of external stimuli,
population activity can exhibit complex self-organized patterns [6]. Its complex nature and general similarity with activity evoked by sensory input [7–10] suggests that spontaneous activity may play an important role in information processing [11, 12]. By studying spontaneous activity, a lot has been learned about the structure of cortical population spike patterns. During resting and sleep, cortical circuits (both in vitro and in vivo) spontaneously produce periods of activity known as “upstates” [13–17]. In vitro experiments have shown that neural activity within upstates has a sequential structure, with the order in which neurons fire largely conserved from one upstate to the next, reflecting the interaction of recurrent circuitry and intrinsic cellular dynamics [10, 18, 19]. Early evidence for sequentially structured spiking activity in vivo came from studies detecting the presence of precisely repeating spike motifs [20]. However, the statistical methods employed, as well as the long duration and high temporal precision of the detected motifs, have been controversial [21–23]. Recent analyses of in vivo population data have confirmed using straightforward statistical methods that population bursts such as upstates are indeed sequentially patterned for a period of the order of 100 ms, with temporal precision decaying as the upstate progresses [14].

Here we summarize a series of recent studies conducted by the author, describing the fine structure of sensory responses and spontaneous activity. By simultaneously recording from tens of neurons, it has been found that neuronal activity is composed of transient but coherent and structured bursts of population activity, which we termed “packets.” Firstly, we will describe how packets contribute to the global structure of population activity. Next, we will analyze the sequential structure of packets and show how it is conserved across different brain states. We will then describe how sequential structure of packets encodes information about sensory stimuli. In the following sections, we will discuss possible mechanisms of packet formation and present a graphical summary of the main results. Lastly, we will describe how the concept of a packet can provide unifying model for neuronal coding, which binds together multiple seemingly contradictory observations about information processing.

Cortical Activity Is Composed of Population Activity Packets

The brain exhibits different patterns of activity depending on the behavioral state. On one extreme is a synchronized brain state which occurs during slow wave sleep or during deep anesthesia, where bursts of population activity called upstates are interspersed with periods of global neuronal silence (downstates) [17]. On the other extreme, when an animal is attentive to a task or stimuli, cortical activity is in desynchronized state, which is characterized by seemingly continuous population activity. This variability in cortical state can be also observed in quiescent waking animals [16, 24], which is illustrated in Fig. 8.1a. Note that even in a desynchronized state (Fig. 8.1a-bottom), population activity still exhibits coordinated 50–100 ms long
Fig. 8.1  Population activity in the auditory cortex shows coordinated bursts of activity (packets). (a) Examples of raster plots with periods of spontaneous activity followed by periods with tone presentation. Data recorded in auditory cortex in awake rat. Plots are sorted by cortical state. The raster shows spikes of simultaneously recorded neurons and the blue trace shows local field potential. At the bottom of the figure is the multiunit firing rate (MUA) computed as the smoothed summed activity of all neurons. Note that neurons tend to fire in transient bursts of 50–100 ms duration, with burst times including but not limited to tone onset. Activity during desynchronized states shows weaker global fluctuations but still exhibits complex fine structure. To visualize sequential activity within packets, neurons are sorted by latency in the same order in all three panels (see following section and Fig. 8.2f for more details). (b) Histogram of instantaneous MUA rates during sustained tone responses for desynchronized and synchronized trials. Dotted lines indicate the same analysis for trial-shuffled data. (c) Top of the panel shows examples of population rate on three single trials. Note that activity packets occur reliably at tone onset but sporadically during spontaneous and sustained periods. Bottom of the panel shows the trial-averaged population rate triggered at tone onset. (d) Box-and-whisker plots summarizing distributions of onset-evoked packets, and the distribution of amplitudes of the largest packets in the sustained and spontaneous periods. The central mark is the median, the edges of the box are the 25th and 75th percentiles. (e) Probability of occurrence of large activity packets (mean + 2 SD) during spontaneous, onset, and sustained periods. These analyses suggest that packets have similar amplitude for onset, sustained, and spontaneous periods but occur more reliably at stimulus onset. Figure reproduced from [24]
bursts which are also accompanied by a deflection of local field potential (LFP). These bursts are larger than expected from random fluctuation in firing rate, which is illustrated in Fig. 8.1b. This figure shows histograms of the distribution of population firing rate for the synchronized and desynchronized states (solid lines) as compared to trial-shuffled data (dashed lines) [24]. For synchronized data, the histogram (blue) shows a clear mode at 0, indicating the presence of prolonged down phases, and a “tail” corresponding to large bursts of activity. For desynchronized trials, the distribution of multunit (MUA) was less skewed but still markedly different from the shuffled data, confirming the existence of smaller but still significant population bursts in the desynchronized state ($p<0.001$ two-sample Kolmogorov-Smirnov test). We will call these population bursts “packets” to emphasize that each population burst has a fine-scale organization that carries stimulus-specific information, which we will describe in the following sections.

**Activity Packets Occur More Reliably at Stimulus Onset but Are Not Larger than During Sustained or Spontaneous Periods**

We will begin analyzing packets by looking at onset responses evoked by sensory stimulation. Figure 8.1c (top) plots the population rate in the auditory cortex for 3 trials with tone presentations. It suggests that the packets of activity accompanying tone onsets are not larger in amplitude than those occurring either within extended tone presentations or in silence. This might at first appear to contradict the fact that one sees clear onset responses when activity is averaged across multiple trials (Fig. 8.1c-bottom). The reason for this is that onset responses in averaged activity occur not because the activity packets triggered by tone onsets are larger than those occurring spontaneously or during sustained tone epochs but because activity packets are reliably evoked by tone onsets and occur at random times during sustained tone responses and spontaneous activity. To quantify this, we calculated, for each tone presentation, the height of the population rate peak after stimulus onset (0–100 ms), the height of the highest population rate peak in the preceding period of silence (−800–0 ms, to avoid offset responses from the previous tone), and the highest population rate peak in the sustained response period (200 ms–1 s after tone onset). Statistical test revealed that population rates at onset were significantly smaller than the highest peaks during 800 ms immediately before or after onset response at each trial (Fig. 8.1d; rates are expressed as z-scores to combine data from different experiments; $p_{\text{onset-\text{sust}}}$, $p_{\text{onset-\text{spont}}}<0.0001$; $p_{\text{sust-\text{spont}}}$ = 0.2, two-sample Kolmogorov-Smirnov test; [24]). This indicates that the population was typically more active at some moment during the sustained period or silence preceding each tone than at onset. However the probability of seeing an activity packet (measured as an instantaneous MUA rate larger than the mean + 2 SD) was significantly higher at onset as compared to any time point during spontaneous or sustained periods.
To verify that these results did not simply occur from occasional random spiking coincidences during the sustained and spontaneous periods (which are longer than the onset periods), we performed the same analyses on trial-shuffled data. This confirmed that the detected activity packets reflected true synchronous firing events \[24\]. Therefore, we concluded that the onset responses seen in activity averaged across trials reflect a stimulus-locked increase in the probability of activity packets, rather than an increase in their size.

Similarity of Sequential Spiking Activity of Stimulus-Evoked and Spontaneous Packets

So far we have only looked at population activity which reflects the sum of activity of all recorded neurons. Next, we will examine more closely the activity of individual neurons within packets and begin again by analyzing onset responses. Figure 8.2a–c shows raster plots and superimposed peri-event time histograms (PETHs) of three individual neurons in response to five different tones. Although the firing rate evoked in any given neuron varied with tone frequency, PETH shapes were largely conserved across tone frequencies. However, between neurons, PETH shapes differed considerably. To quantify the preservation of temporal structure across stimuli, we computed for each PETH a mean spike latency (MSL), defined as the mean spike time in the 100 ms after stimulus onset \([9]\). Figure 8.2d plots each neuron’s MSL to its preferred tone frequency versus its average MSL to all other tones. For neurons with short latency (MSL below 40 ms for best frequency), the majority of points are below the diagonal, suggesting that for such neurons preferred stimuli often induce earlier firing \((p<0.001,\text{ paired Wilcoxon signed rank test})\). Robust correlation between MSL for preferred and non-preferred tones \((R=0.72\pm0.24; p<0.001)\) confirms that temporal profiles are diverse between neurons and largely conserved within the responses of each cell to different tones. Thus, if a neuron is driven to fire in response to a given tone, it will do so with a stereotyped cell-specific temporal profile but with precise timing and firing rate affected by stimuli.

Next, we asked whether spike patterns within spontaneously occurring packets are also temporally structured as packets evoked by sensory stimuli. Figure 8.2e (top) shows raster plots of two of the individual neurons’ responses evoked by tone onset, and Fig. 8.2e (bottom) shows average activity of 30 simultaneously recorded neurons to tone stimuli. For comparison, Fig. 8.2f shows raster plots and PETHs of the same neurons as in Fig. 8.2e, triggered at the beginning of spontaneously occurring packets (upstates). Again, a similar sequential ordering was seen. To statistically confirm this similarity, a slightly different approach was used, as the beginnings of spontaneous packets are not experimentally controlled. To measure a cell’s position in the firing sequence within a packet, we defined a measure \(\mu_{cc}\), the center of mass of its cross-correlogram with the summed activity of all other neurons within
Fig. 8.2  Similarity of stimulus-evoked and spontaneous packets of sequential spiking activity. (a–c) Raster plots showing responses of representative neurons to presentations of 5 pure tones (100 trials for each tone). Red lines represent peri-stimulus time histograms. It shows that individual neurons respond to different tones with stereotyped temporal profiles but varying firing rates. (d) Scatterplot showing each neuron’s mean spike latency to its preferred tone frequency versus to all other tones. The red line corresponds to equal latencies. Blue dots represent putative interneurons as defined by spike width. While neurons typically show earlier firing to their preferred tone, this difference is an order of magnitude smaller than the differences between cells. (e-top) Raster plots showing spike times for two representative neurons to repeated presentations of a pure tone stimulus. (e-bottom) Average activity of 30 simultaneously recorded neurons to tone stimuli. Gray bars show pseudocolor representations of each neuron’s peri-event time histogram (PETH); red dots denote each neuron’s mean spike latency in the 100 ms after tone onset. Neurons are ordered vertically by the mean latency over all stimuli to illustrate sequential spread of activity. (f) Raster plots and average activity for the same neurons as in panel (e), triggered by upstate onsets. Note the similar temporal pattern to panel (e). (g) Normalized cross-correlograms of one neuron’s spike times with the summed activity of all other cells. Arrow shows the center of mass (mean spike time) of correlograms ($\mu_{cc}$). (h) Conservation of $\mu_{cc}$ across different stimuli and spontaneous events, indicating preservation of sequential order. Each point represents the values of $\mu_{cc}$ for a given cell in the conditions indicated on the axes. Reprinted from Neuron, 62(3), Luczak A, Barthó P, Harris KD, Spontaneous events outline the realm of possible sensory responses in neocortical populations, 413–425, copyright 2009, with permission from Elsevier.
±50 ms (Fig. 8.2g; see Experimental Procedures in [9]). Values of $\mu_{cc}$ were correlated between spontaneous events and stimulus classes, demonstrating that firing order is consistent between stimulus-evoked packets and spontaneous packets (Fig. 8.2h; $R_{unanesth, spont-ton} = 0.53 \pm 0.17; p < 0.001$). Similar consistent temporal patterns were also observed in the somatosensory cortex [9] and in the visual cortex [25] indicating that the sequential structure of spontaneous and evoked packets is a general feature of cortical processing.

Sequential Packet Structure Is Robust with Respect to Different Brain States

Patterns of population activity can change substantially with brain state as illustrated in Fig. 8.1a (compare top and bottom rasters). Does this change in population pattern also affect the internal structure of packets? To investigate this question, we again employed cross-correlation analyses between a single neuron and MUA as illustrated in Fig. 8.2g, i. We found that cross-correlograms calculated separately during synchronized and desynchronized brain states had similar temporal profiles. Figure 8.3a, b shows the cross-correlograms for 45 neurons recorded simultaneously, with the order of neurons sorted by $\mu_{cc}$ measure in the synchronized state and the desynchronized state, respectively. $\mu_{cc}$ was strongly correlated between these states (Fig. 8.3c; $R = 0.67 \pm 0.23$ SD). This shows that packets in the synchronized and desynchronized states have largely preserved sequential spiking patterns. This also suggests that activity in both states is composed from the same type of packets, but in a desynchronized state, the time between consecutive packets decreases and creates an impression of continuous spiking patterns.

Relation to Local Field Potential (LFP)

The above analyses have indicated that a given neuron fires with largely stereotypical timing relative to the 50–100 ms long activity packets regardless of brain state. Because summed population activity is strongly correlated with the (negative) local field potential (as seen in raw data in Fig. 8.1a), we would expect that a neuron’s timing with respect to these packets was related to its phase of firing with respect to the LFP. Figure 8.3d shows examples of the cross-correlogram of the same neuron with MUA (equivalent to spike-triggered MUA) and with LFP (Fig. 8.3e) in the synchronized and desynchronized states. It shows that this neuron fired after the majority of other neurons and after the maximum deflection in LFP in both states. The relationship between the $\mu_{cc}$ measure and LFP phase for simultaneously recorded neurons is presented in Fig. 8.3f; $R_{syn} = 0.73 \pm 0.17$ SD, $p_{syn} < 0.05$, circular-linear correlation [26]. It indicates that the importance of spike timing in relation to the LFP phase which was recently reported [27] could be the consequence of the sequential organization of activity packets.
Fig. 8.3  Sequential spiking order within packets is preserved across different brain states. (a, b) Pseudocolor representation of CCGs for all neurons of a representative experiment, during synchronized (a) and desynchronized (b) periods. Each horizontal line of the pseudocolor matrix corresponds to the CCG of one neuron, vertically arranged in the same order for each plot, according to the value of $\mu_{cc}$ in the sustained period. For visualization, CCGs are normalized to mean 0 and unit variance. (c) $\mu_{cc}$ for each neuron calculated during sustained tone responses, in synchronized and desynchronized trials. Neurons from different animals are shown with different colors. The distribution of points along the equality line shows that each neuron’s temporal relationship to the population is preserved across states. (d) Spike-triggered MUA histogram for an example neuron and (e) spike-triggered LFP for the same neuron during synchronized (blue) and desynchronized (red) brain state. Note that the (negative) peak of this curve occurs at a similar time to the peak of the spike-triggered MUA in the top panel. LFP was band-pass filtered between 8 and 12 Hz. (f) Relation between $\mu_{cc}$ and mean LFP phase at 8–12 Hz. Each dot represents a single neuron. It shows that the phase relationship of spike timing to LFP mirrors the timing relationship to population activity. (g) Representative examples of upstate-triggered LFPs sorted by first peak amplitude from a single shank. (h) Cross-correlogram between a single neuron and multiunit activity during first 150 ms of upstates for putative pyramidal cells (activity of the analyzed cell is triggered at multiunit activity spikes). Note that each cell has a different timing relation to multiunit activity but that the timing relation is similar for upstates with and without 12 Hz modulation. (i) The same analysis for putative interneurons. As compared to putative pyramidal cells, putative interneurons show a less diverse timing in relation to multiunit activity. (j) Comparison of latencies calculated for upstates with and without 12 Hz modulation (latency is defined as the center of mass of the cross-correlogram; [28]). Red and blue dots denote putative interneurons and putative pyramidal cells, respectively. Distribution of points along the identity line (dashed) shows that regardless of upstate type, neurons have a consistent temporal relation to population activity. Figure reproduced from [24, 28]
Fig. 8.4  Spike precision and information coding within packets. (a) For every trio of neurons, a spike triplet is described by two inter-spike intervals ($t_2-t_1$ and $t_3-t_1$). (b) Count matrix for a representative triplet of neurons, indicating the probability of different ISI combinations. **Black square** denotes triplets occurring within ±10 ms of the mode. (c) Triplet structure reflects individual neural latencies. Each triplet is represented by two points: (latency of neuron 2–latency of neuron 1 and latency of neuron 3–latency of neuron 1). The strong correlation indicates that the structure of the triplets is predicted by the sequential structure of packets. (d) Occurrence of precisely repeating triplets peaks shortly after the start of UP states. **Blue and red curves** denote shuffled data for independent Poisson and common excitability models, respectively (the dashed lines indicate SD; [14]). (e) Spike timing reliability measure decays as a function of time after packet onset. Line width indicates the size of smoothing kernel. (f) Sequential structure of activity packets depends on tone frequency. Sequential similarity was measured as the correlation coefficient of $\mu_{cc}$ across the population for all pairs of tone frequencies. Note that the greatest similarity is seen between responses to different presentations of the same frequency (distance 0), whereas a smaller but nonzero similarity is seen for widely separated tone frequencies (distance 5). (g) Percentage of cells in the auditory cortex showing significant excitatory response to at least one tone stimulus, as a function of peri-stimulus time [54]. **Purple line** denotes sustained epochs. (h) Fraction of spikes, time-locked to population activity during sustained periods of tone presentations. Higher spike-locking values for the majority of neurons as compared to shuffled data (gray line) show that during sustained period neurons prefer to fire spike time-locked to packets [24]. Figure reproduced from [14, 24].
Another example of strongly preserved sequential packet structure can be found in somatosensory cortex of ketamine-anesthetized rats, where population activity patterns occurring at ~1 Hz can switch to faster ~12 Hz oscillatory patterns (spindles) [28]. Figure 8.3g illustrates representative examples of upstate-triggered LFPs during periods with and without 12 Hz oscillations (denoted by pink and green colors, respectively). To examine in more detail the temporal relationship between neurons’ activity during different types of upstates, for each neuron, we calculated its cross-correlogram with MUA, as described in the previous section. Figure 8.3h, i shows such sample cross-correlograms for both periods, for representative pyramidal cell and for representative interneuron, respectively [29]. Cross-correlograms had similar skewness for upstates with and without 12 Hz modulation, which was also the case for the majority of recorded neurons (Fig. 8.3j; \( R=0.59, p<0.01 \)). This shows that even with drastic changes in oscillatory brain activity, temporal relations between neurons with ±50 ms window are remarkably stable, suggesting highly conserved sequential structure within packets.

### Spike Precision and Information Coding

#### Precisely Repeating Spike Triplets

We have seen that neurons display consistent temporal relationships within packets, indicating that certain precise spike patterns should occur above chance level. Precisely repeated spike patterns have been reported in a number of cortical systems [10, 18, 19, 29–31], although the interpretation of these results has been controversial [21, 23]. We hypothesized that the consistent timing of individual neurons in relation to the onset of a packet could account for precisely repeating spike patterns seen at the population level. Confirmation of this hypothesis would provide both convincing evidence for the precise repetition of spike patterns and a simple explanation for it.

For computational tractability, we restricted our search to spike triplets occurring across three distinct cells [32] (Fig. 8.4a). For each cell trio, one cell was designated the trigger for calculation of the joint distribution of spike times of the other two [32]. Often, a clear mode was seen in these plots, suggesting that a particular sequence occurred preferentially (e.g., Fig. 8.4b). The location of the mode could be predicted from the neurons’ individual latencies to packet onset (Fig. 8.4c). Note that spiking precession is not within 1 ms; therefore these results are not fully consistent with the concept of “synfire chains” which generally implies repeating patterns to have a millisecond-level precision [20]. Repeating triplets (defined as those whose inter-spike intervals (ISIs) were within ±10 ms of the mode, indicated by the black square in Fig. 8.4b) occurred preferentially shortly after UP state onset (Fig. 8.4d), with the highest precision of spikes at the beginning of the packets (see
Fig. 8.4e showing reliability of spiking over time; method adopted from [33]). This finding is consistent with [34] where the highest spiking precision was found shortly after stimulus onset and decreased thereafter. Therefore, we conclude that the timing and structure of repeating triplets is predicted by the relationship of individual neurons to packet onsets.

**Temporal and Firing Rate Coding Within Packets**

It is well documented that sensory stimuli can affect spike timing, especially for onset responses (see Fig. 8.2a or, e.g., [35]), but it is not clear if packets also show modification of temporal structure depending on stimulus. Thus, we next asked whether different tone stimuli caused variations around this common sequential structure. To test this idea statistically, we assessed the similarity of the sequential structure between the first and second half of the data set. Figure 8.4f shows the mean sequence similarity as a function of distance between frequencies, based on tonal order. Sequences become less correlated with increasing frequency difference between tones (Fig. 8.4f; \( R = -0.22 \pm 0.08 \) SD) which was not observed for shuffled data [24]. Thus, as observed with onset responses, even during sustained periods, the packets have a broadly conserved 50–100 ms sequential structure, but this structure exhibits further variations depending on tone frequency.

It is also well documented that information about external stimuli can be encoded by the firing rates of neurons. Closer examination of population activity revealed that in response to preferred stimuli, a neuron fires additional spikes but only when it is coordinated with the activity of other neurons. As an example, let’s consider the population activity during sustained tone presentations which is composed of packets of activity as illustrated in Fig. 8.1. Theoretically, the extra spikes evoked by preferred stimuli could occur uniformly throughout the tone presentation, without regard to global network activity, or alternatively, extra spikes could occur specifically during packets of high network activity (“time-locked” to packets). To address this question, we estimated the fraction of spikes locked to packets during sustained tone presentation (Fig. 8.3g). For this, we used a measure-based MUA cross-correlogram with single neuron activity normalized by an autocorrelogram (for details, see [24]). Figure 8.3h shows values of the fraction of spikes time-locked to packets, which is significantly larger than would be expected for trial-shuffled data (\( p < 0.001 \)). Thus, this analysis suggests that the additional spikes a neuron fires in response to its preferred tone are primarily occurring at neuron-specific timing within packet.

**Possible Mechanisms of Packet Formation**

Sequentially structured activity packets are seen in computational models of cortical circuits [36–38], in cortical slices [10, 19, 39], as well as in response to sensory stimuli in vivo [9]. We found that population responses to different stimuli are
subject to conserved spatiotemporal constraints, consistent with results in other
modalities indicating conserved timing patterns in pairwise cross-correlograms
[25]. One can imagine a number of ways in which the physical properties of a neural
circuit could impose consistent constraints on the spike patterns it can generate.
Firstly, cortical neurons have diverse intrinsic physiological properties [40–42]
which may contribute to the consistent cellular timing which we and others observed
[14, 43]. For example, cells with lowest threshold could be firing earliest in sequence
[44]. Secondly, connectivity within cortical circuits is far from homogenous, for
example, with strong reciprocal connectivity occurring more than expected by
chance [45], suggesting that the stereotypical temporal structure of cortical activity
packets may be also imposed by the connectivity of the cortical microcircuit. We
suggest that these activity patterns are the functional manifestation of “default
microcircuits”—local patterns of connectivity that impose similar spatiotemporal
constraints on spontaneous and stimulus-evoked flow of activity, as illustrated in
cartoon form in Fig. 8.5a [46].

Summary Illustration of Packets

Our main findings can be summarized by Fig. 8.5. Connectivity and cellular proper-
ties of neurons impose constraints on types of spiking patterns which can be pro-
duced by the local circuit (Fig. 8.5a). Thus, certain activity patterns will be more
likely to emerge than other patterns (Fig. 8.5b—left). This can be illustrated as geo-
metrical interpretation, where each population spiking pattern is represented as a
single point (Fig. 8.5b-center). Experimentally observed spontaneous patterns are
confined only to a small subregion of space of all possible patterns. Stimulus-evoked
patterns are subject to the same circuit constraints and form subspace within spon-
taneous patterns [9]. Each type of stimuli results in a different firing rate of neurons,
and to a smaller degree different timing, but with preservation of the overall struc-
ture within the activity packet (Fig. 8.5b—right).

In synchronized states, stimulus onsets usually evoke reliable activity packets
with a duration of 50–100 ms, and similar packets occur irregularly during sus-
tained tone responses and spontaneously (Fig. 8.5c). As described above, these
packets have a broadly preserved sequential structure across stimuli and across
onset, sustained, and spontaneous periods. However, both the firing rates and pre-
cise timing of the constituent neurons can vary with stimulus type (Fig. 8.5b-right).
The additional spikes fired in response to preferred stimuli occur within packets
rather than spread evenly throughout the stimulus duration. In desynchronized
states, fluctuations in population rate are reduced, but timing relationships between
neurons remain preserved (Fig. 8.5d). This suggests that population activity is built
from discrete packets whose content conveys information about the stimulus, occur-
ring reliably at onset and irregularly at other times, with desynchronized activity
consisting of multiple overlapping packets rather than continuous, unstructured
activity as previously assumed.
Fig. 8.5 Activity packets in graphical summary. (a) Cartoon illustration of the possible mechanism of packet formation. Due to constraints on connectivity, different inputs will result in similar spiking activity, which propagates preferentially through the strongest connections (solid arrows) embedded in a pool of weaker connections (dashed arrows). As a consequence of the connectivity pattern of the network, certain activity patterns are more likely to occur than others as illustrated in panel (b) (left side). (b-center) Cartoon illustrating the geometrical interpretation of our findings. The gray area illustrates the space of all spiking patterns theoretically possible for a packet. The white area represents the space of spontaneous packets; this is shown elongated and of small volume to illustrate strong constraints on patterns of activity imposed by a network. Packets evoked by different stimuli occupy smaller subsets within this (colored blobs). (b-right side) Illustration of stimulus-evoked packets. The overall structure of evoked packets is similar to the spontaneous packets; but the firing rate, and to a smaller degree, the spike timing of neurons, encodes information about stimulus identity. (c) Packets of population activity in a synchronized state are separated by periods of global silence. Tone onset reliably induces an activity packet, but packets also occur sporadically throughout the sustained and spontaneous periods. Within each packet, neurons fire with a stereotyped sequential pattern. Presentation of a neuron’s preferred tone causes that neuron to fire at higher rates (red) but only during specific phase of activity packets. (d) In a desynchronized state, population activity does not show long periods of silence, but temporal relationships between neurons are similar to those in the synchronized state. This can be explained by a model in which many packets, individually similar to those seen in the synchronized state, are superimposed to produce a firing pattern that exhibits smaller fluctuations in global activity but retains a fine temporal structure. Figure reproduced from [24, 46]
Packet Structure May Explain Multiple Puzzling Observations About Neuronal Coding

Below we address the significance of packets. We list some of the most puzzling phenomena about neuronal coding, and we discuss how it could be understood in light of the sequential structure of packets. We argue that the “packet theory” presented here could provide a unifying concept on how information is processed in the brain.

– A packet structure provides time reference for temporal coding. It was shown that precise timing of spikes after stimulus onset can provide information about stimulus identity [35, 47]. Although an experimenter knows what the exact time of a stimulus onset is, it remains unclear how the brain could access this information to use spike timing in reference to onset. It was proposed that there could be neurons always firing with the same latency to any stimuli, thus providing reference for decoding information from spikes in which timing differs with stimuli [48]. Considering that many natural stimuli change gradually and do not have well-defined sharp onset, the above-described mechanism may not have general applicability. On the other hand, assuming that there exists a “typical” or “default” sequential activity pattern imposed by cortical microarchitecture, any variation in timing among neurons in this sequence can encode stimuli. Therefore, the “default” temporal structure of a packet can provide reference for the brain to interpret the timing of neurons.

– Packets show how temporal and firing rate coding coexists. As illustrated in Fig. 8.5b-right, in response to preferred stimuli, a neuron fires more spikes, but it is mostly restricted to the neuron-specific phase within a packet.

– Packets and cell assembly hypothesis. The idea introduced by Donald Hebb in the 1940s [49] proposes that neurons are active collectively in groups produced by Hebbian plasticity. Furthermore, Hebb postulates that different stimuli are represented by unique neuronal assemblies with completely different temporal patterns depending on task or stimulus. However, evidence for the conserved structure of packets necessitates a partial revision of Hebb’s theory. Specifically, conserved activity patterns imply that neuronal assemblies are like a variation on a one master theme rather than unique themes for each stimulus or object. For example, auditory neurons in Fig. 8.5b (right) respond with similar temporal sequences to different tones, although each tone evokes a different variation of that pattern [9].

– Stereotypical activity within packets provides an explanation as to why precisely repeated spiking pattern can occur significantly more often than expected by chance [20, 29].

– Preplay. In behaving animals, task-induced patterns of neuronal activity are replayed during following rest which is believed to be a hallmark of memory formation [50]. Recent studies have shown that replayed patterns are also similar to spontaneous patterns that precede behavioral task. This phenomenon is termed
“preplay” and was elegantly shown in the hippocampus by [51]. Similarly, in ([52], Figure 1, 2007), the pre-task spiking patterns in the medial prefrontal cortex have an obvious similarity to patterns during the task and patterns replayed after the task. The data presented here is consistent with these results. Due to the connectivity constraints of local microcircuits, new experience does not create completely different patterns, but rather creates modification of existing patterns. Such task-induced gradual change of existing spiking patterns results that general structure of activity packets is preserved [53]. Also note that the timescale of preplayed and replayed patterns spanning up to a few hundred milliseconds is similar to the duration of packets. Thus, we hypothesize that memory replay could be the manifestation of, as described here, packets carrying information about past experience.

**Function of Packets**

What could be the function of the sequential structure of packets? One perspective could be that it has no function as the system has to generate sequential patterns given the constraints imposed by network connectivity [46]. A different possibility from an engineering point of view could be that dividing neuronal activity in packets could serve similar function as Internet protocol (IP) packets, where splitting data in small chunks with a specific format improves communication efficiency and transmission reliability. Indeed, it was observed that in the brain constraining spiking activity to small temporal windows (e.g., only to a negative phase of underlying oscillatory activity) can improve information transfer between areas by synchronizing neuronal firing, and that mechanism is commonly used across the brain [11]. Moreover, there are evidences that sequential organization of activity within packets may also have functional significance. For instance, broad tuning and highest spiking precision at the beginning of a packet may be designed to signal the beginning of a message with only general information about stimuli (roughly analogous to header of IP packets). Consequently, later activity within a packet may contain more precise information. Indeed, it was observed that activity that occurred later after stimulus onset is more stimulus specific, with finer tuning of neurons [54, 55], likely due to top-down modulation [56]. In result, our perception of continuous stimuli may be an illusion, as cortical activity may carry information not continuously, but rather in a form of discrete and structured packets.

**References**


## Author Queries

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