

# Clustering of neural code words revealed by a first-order phase transition

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A network of neurons in the central nervous system collectively represents information by its spiking activity states. Typically observed states, i.e., code words, occupy only a limited portion of the state space due to constraints imposed by network interactions. Geometrical organization of code words in the state space, critical for neural information processing, is poorly understood due to its high dimensionality. Here, we explore the organization of neural code words using retinal data by computing the entropy of code words as a function of Hamming distance from a particular reference codeword. Specifically, we report that the retinal code words in the state space are divided into multiple distinct clusters separated by entropy-gaps, and that this structure is shared with well-known associative memory networks in a recallable phase. Our analysis also elucidates a special nature of the all-silent state. The all-silent state is surrounded by the densest cluster of code words and located within a reachable distance from most code words. This code-word space structure quantitatively predicts typical deviation of a state-trajectory from its initial state. Altogether, our findings reveal a non-trivial heterogeneous structure of the code-word space that shapes information representation in a biological network.

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## I. INTRODUCTION

Recent advances in multi-electrode recording techniques allow simultaneous measurements of neural activity from a large population of interacting neurons [1,2]. A population of neurons encodes various information by its collective spiking activity patterns, namely, neural code words [3]. These code words are passed and interpreted by a downstream circuit for further information processing. Characterizing the organization of the code words is therefore critical for our understanding of neural coding.

To characterize the distribution of code words, a maximum entropy model [4] with pairwise interaction terms has been fitted to neuroscience data [5,6]. This model that fits the first two moments of activity statistics was reported to characterize real data well in small groups of neurons. Importantly, these studies also suggest that code words are restricted due to neural interactions within a small subset of the state space, namely, the space composed of all possible combinations of each neuron's binary activity. However, the geometrical organization of code words is not well understood.

Interestingly, the code words of the well-known Hopfield network [7] are also restricted within a small subset of state space due to strong constraints imposed by interactions between neurons. The state space of the Hopfield network is organized into multiple basins of attraction [8], with which a simple Glauber dynamics [9] can recall one of memorized patterns hinted by a distorted initial pattern. This is the so-called associative memory [7,8]. Although both the neuroscience model described above and the Hopfield network belong to the pairwise maximum entropy model, it remains largely unknown if their code-word spaces, composed of all code words, share common features. Recent investigation of retinal activity data revealed multiple local energy minima (LEM) in a fitted maximum entropy model [10]. However, it

does not provide how neural code words are geometrically organized because demonstration of the code-word space structure entails consideration of all possible states.

The high dimensionality of the state space prevents an exhaustive search except in small networks, and standard dimensionality-reduction techniques can easily abolish underlying structure by neglecting many relevant dimensions. Hence, an efficient new technique is in need to visualize the neural code-word space. One insight is that distance between code words is an important factor that constrains neural dynamics—previous experiments have shown that state transitions are mostly restricted to neighboring code words and nearby code words are known to encode similar information [11,12]. Based on this observation, we propose the distance-constrained statistical mechanics analysis [13,14] to concisely characterize the code-word space structure based on the distance from a reference code word. In particular, we present an advanced mean-field framework that computes the entropy of code-words as a function of Hamming distance from any reference state. By applying this technique to both the Hopfield network and retinal data, we explore their code-word space structures, i.e., whether code words are divided into multiple clusters.

## II. RESULTS

### A. Distance-constrained statistical mechanics analysis

We first introduce a statistical mechanics framework to characterize code word organization in the state space. Let  $\sigma_i$  be binary activity of neuron  $i$  ( $i = 1, \dots, N$ ) and  $\sigma = (\sigma_1, \dots, \sigma_N)^T$  be a state vector, representing population activity of  $N$  neurons. Here  $\sigma_i = 1$  indicates that neuron  $i$  is active and  $\sigma_i = -1$  indicates that neuron  $i$  is silent. The symbol  $^T$  represents the transpose operation.

According to the maximum entropy principle [4], the activity state follows the Boltzmann distribution  $P(\sigma) \propto \exp(-\beta E(\sigma))$ , where  $\beta$  is the inverse temperature or neural reliability ( $\beta = 1$  unless otherwise indicated) and the energy

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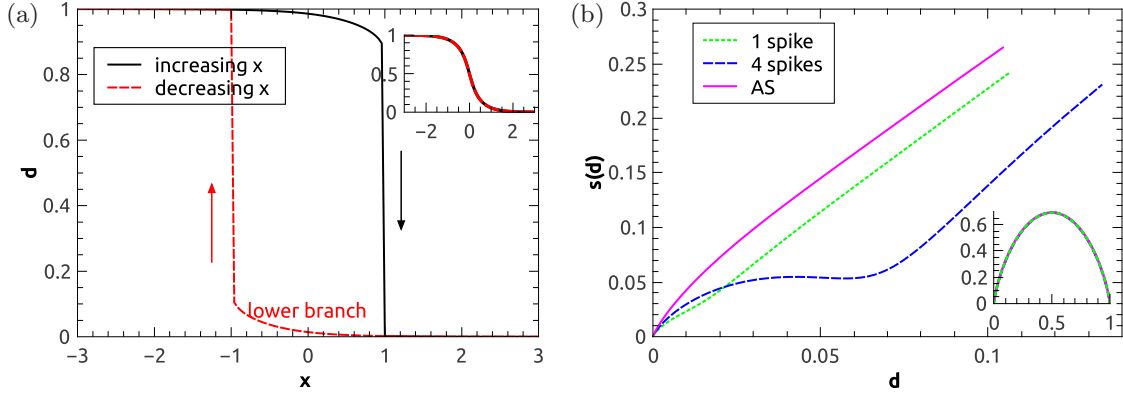


FIG. 1. Code word organization of standard Hopfield model ( $P = 3$ ) with low spiking rate constraint of stored patterns. (a) A first-order phase transition in Hamming distance  $d$  when the coupling field  $x$  is tuned. The reference pattern is the one with four spikes [see (b)]. The inset shows that the first order transition vanishes in the high temperature regime ( $\beta = 0.2$ ). (b) entropy per neuron as a function of Hamming distance from a reference stored pattern with different spike-counts. The pattern with zero spike-count is named all-silent (AS) state. The curves correspond to the low- $d$  branch of the hysteresis loop [see (a)]. The inset shows a trivial entropy landscape identical for all references in high-temperature regime.

$E(\sigma) = -\mathbf{h}^T \sigma - \frac{1}{2} \sigma^T \mathbf{J} \sigma$ .  $\mathbf{h}$  denotes a spiking bias vector and  $\mathbf{J}$  a functional coupling matrix. Geometrical organization of code words is studied by introducing a modified probability distribution  $P(\sigma) \propto \exp(-\beta E(\sigma) + x \sigma^T \sigma^*)$ , where coupling field  $x$  is introduced to control the overlap  $\sigma^T \sigma^*$  between state  $\sigma$  and reference one  $\sigma^*$ . This perturbed probability measure gives the free energy per neuron defined by

$$\begin{aligned} f &\equiv -\frac{1}{\beta N} \log \sum_{\sigma} \exp(-\beta E(\sigma) + x \sigma^T \sigma^*) \\ &= -\frac{1}{\beta N} \iint d\epsilon dq \exp(-N\beta f(\epsilon, q)), \end{aligned} \quad (1)$$

where

$$\beta f(\epsilon, q) \equiv \beta \epsilon - xq - s(\epsilon, q) \quad (2)$$

is the energy- and overlap-dependent free energy that characterizes the probability of states having energy  $N\epsilon$  and overlap  $Nq$ , and  $s(\epsilon, q) \equiv (1/N) \log \sum_{\sigma} \delta(\epsilon - E(\sigma)/N) \delta(q - \sigma^T \sigma^*/N)$  denotes entropy (log-number of states) per neuron with energy  $N\epsilon$  and overlap  $Nq$ . If the system-size  $N$  is large, the integral in Eq. (1) is typically dominated by a combination  $(\epsilon, q)$  that minimizes  $f(\epsilon, q)$ , i.e.,  $f \approx \min_{\epsilon, q} f(\epsilon, q)$ .

We compute  $\epsilon$  and  $q$  that minimize  $f(\epsilon, q)$  by applying the Bethe approximation [15] (see the Appendix). By recursively solving the mean field equation, we estimate a local (or global) minimum of the free energy and  $(\epsilon, q)$  corresponding to this minimum. Notably, these values of  $\epsilon$  and  $q$  characterize the energy and overlap of typically observed states (namely code words), respectively. Meanwhile, the entropy of code words  $s(\epsilon, q)$  can be also computed according to Eq. (2). We define Hamming distance  $(N - \sigma^T \sigma^*)/2$  that counts how many neurons have distinct activity in state  $\sigma$  and reference state  $\sigma^*$ . The typical value of the overlap  $q$  can be transformed to the typical value of Hamming distance per neuron  $d = (1 - q)/2$ . In the following sections, we omit the  $\epsilon$  dependency of the entropy and report it as a function of  $d$ , i.e.,  $s(d)$ .

## B. Clustering of code words in the Hopfield model

Using the mean field method, we first investigate the structure of code-word space in the Hopfield network [8,16]. In this model, the coupling between neuron  $i$  and  $j$  is constructed as  $J_{ij} = 1/N \sum_{\mu=1}^P \xi_i^{\mu} \xi_j^{\mu}$  for a network of  $N = 60$  neurons, where  $P = 3$  random binary patterns (indexed by  $\mu = 1, \dots, P$ ) are stored. In each pattern, stored activity  $\xi_i^{\mu}$  of neuron  $i$  takes  $+1$  with probability  $r = 0.0338$  and  $-1$  with probability  $1 - r$ .  $r$  is chosen to fit the activity level of retinal neurons we study in the next section. Note that, in the Hopfield model, the neurons have zero spiking bias parameters ( $\mathbf{h} = \mathbf{0}$ ). According to the previous section, we compute the typical distance  $d$  as we increase  $x$  from  $-3$  to  $3$ , and then decrease it from  $3$  to  $-3$  [Fig. 1(a)]. More precisely, after the convergence of the mean field equations at some  $x$ , we change  $x$  by a small amount and restart iteration from the previous fixed point (see the Appendix). The reference state  $\sigma^*$  is set to one of the stored patterns. Remarkably, we find a first-order phase transition of  $d$ , characterized by the hysteresis loop [Fig. 1(a)]. As we decrease  $x$  from high to low values, the typical distance suddenly jumps at around  $x = -1.08$  from  $d \approx 0.16$  to  $d \approx 0.97$ , implying a non-trivial structure of the code-word space.

In order to more directly visualize the non-trivial structure of the code-word space, we plot the entropy of code words computed at various distance  $d$  away from each stored pattern. Only the entropy values corresponding to the low- $d$  branch of the hysteresis loop are shown in the figure. As shown in Fig. 1(b), each stored pattern has a dense core of code words around itself, which discontinuously falls off at some distance. This indicates that code words are organized into multiple clusters, separated by non-code-word states (i.e., gaps). Among three stored patterns, the all-silent (AS) state has the largest core due to the low spiking rate constraint of stored patterns (small  $r$ ).

This clustering results from the attractor structure [16] in the retrieval phase of the model. Within the hysteresis loop, there are two local minima of the free energy [Eq. (2)] competing with each other. Low- $d$  minimum corresponds to the nearby

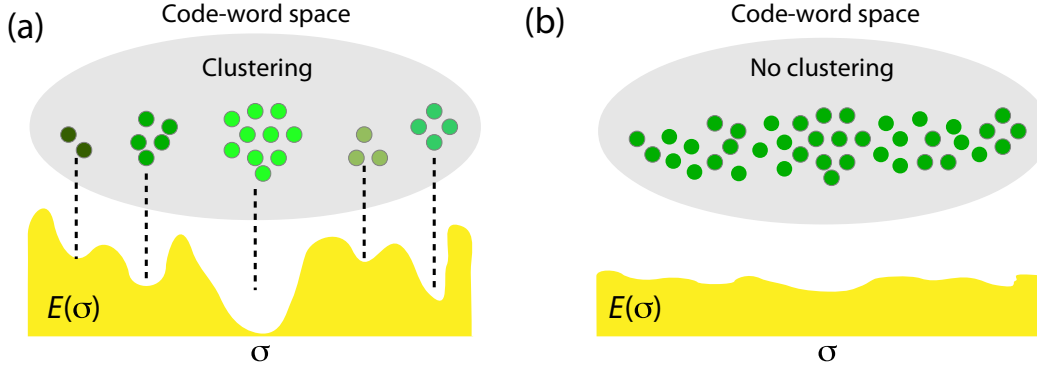


FIG. 2. Schematic illustration of two hypotheses on the organization of neural code words in the state space. Each binary neural code word ( $\sigma$ ) has an energy  $E(\sigma)$ . (a) When neural interactions are strong, neural code words can be organized into multiple clusters in the state space. (b) When the neural population is sufficiently noisy, a trivial structure (a single cluster of neural code words) is observed.

code words of stored patterns ( $\xi$ ), while high- $d$  minimum corresponds to nearby codewords of corresponding reversed patterns ( $-\xi$ ). Thus each stored pattern has distinct entropy landscape surrounding it. The code-word space clustering is necessary for successful memory retrieval in the Hopfield network. In fact, in a high temperature regime (non-recallable phase), the first-order transition and the non-trivial entropy landscape are absent, as observed in the insets of Fig. 1. All reference patterns display the same entropy landscape without entropy gaps, and thus the patterns can not be distinguished from each other. In this non-recallable phase of the Hopfield network, there do exist multiple LEM [see Fig. 2(b)] under greedy descent dynamics (GDD, see the Appendix) on the energy surface, while the code-word space structure is trivial without entropy gaps.

### C. Clustering of code words in the retinal network

The next important question is how code words of a real neural population are organized. To elucidate this question, we analyze spiking activity data of populations of retinal ganglion cells under a repeated naturalistic movie stimulus [10,17]. Although multiple LEM were previously found using this data set [10], it is still unknown if the observed network has clustering of code words or not [Fig. 2(a)]. We therefore characterize the geometrical organization of retinal code words by applying the same method as used in the Hopfield network.

The neural spike trains in a population of  $N$  neurons are binned with a 20 ms temporal resolution to have  $N$ -dimensional spiking states  $\sigma$ . Spiking bias  $\mathbf{h}$  and functional coupling  $\mathbf{J}$  are fitted to the spike train data to reproduce the mean activity and pairwise correlation of the data (see the Appendix). We choose randomly a network sample of the size  $N = 60$  from the neural data (the behavior reported below does not change qualitatively when another sample is chosen, see Fig. 4). Despite no clear similarity in the connectivity structure to the Hopfield network, the retinal network displays the first-order phase transition with a hysteresis loop, qualitatively resembling the Hopfield model [Fig. 3(a)]. This establishes that code words of the retinal network are also clustered. Furthermore, by constructing an independent maximum entropy model, where only the mean activity is fitted to the data with  $\mathbf{J} = 0$ , we show that the first-order phase transition disappears,

indicating that it is the non-trivial neural correlations that shape the clustering of code words.

Figure 3(b) shows the entropy as a function of  $d$  when neural code words of different spike-counts are selected as references. Again, only the entropy values corresponding to the low- $d$  branch of the hysteresis loop are shown in the figure. The high- $d$  branch is not biologically plausible, since the neural code is sparse. The entropy landscape is strongly dependent of the reference. In general, the higher spike-counts a neural code word has, the larger distance its entropy curve extends over, enhancing the ability of the high spike-count code word to come back to the sparse coding regime around the AS state. To quantify this property, Fig. 3(c) plots the maximum distance  $d_{\max}$  at which the low- $d$  branch in the hysteresis loop terminates as a function of spike-counts of the reference code word. We find that  $d_{\max}$  increases linearly with the spike-counts (distance from the AS state) and the estimated slope is  $0.9462 \pm 0.0372$ . The slope close to one is also observed in another typical example (see Fig. 4). Note that the distance to the AS state is typically smaller than  $d_{\max}$ . This implies that, even if the neural code word is far away from the AS state, it still has easy access to the sparse coding regime around the AS state within reasonable time, which highlights the potential role of the AS state [18].

The AS state plays a special role here because the entropy curve from the AS reference state grows much more rapidly as a function of distance than from the other code words [Fig. 3(d)]. Indeed, its growth is close to the upper bound given by the random code word limit [ $s_{\text{ub}}(d) = \frac{1}{N} \ln(\frac{N}{N_d})$ ], in which every state is equally likely. This indicates that the AS state has the densest core of code words around it, which would facilitate frequent visits from other neural code words (see Fig. 5). As previously observed [10], a large portion of neural patterns (about 94.25% of 2000 patterns) are observed to evolve to the AS state by following GDD (see the Appendix).

Figure 3(d) reports the distance-dependent entropy landscape for some reference LEM code words (e.g., state  $a$ ) obtained by running the GDD method starting from corresponding reference non-LEM code words (respectively state  $a'$ ) [see the corresponding multidimensional scaling (MDS) map of LEM in Fig. 6(a)]. The result shows that each reference has a different landscape, and at small  $d$ , the entropy around a non-LEM code word is typically smaller than that for the

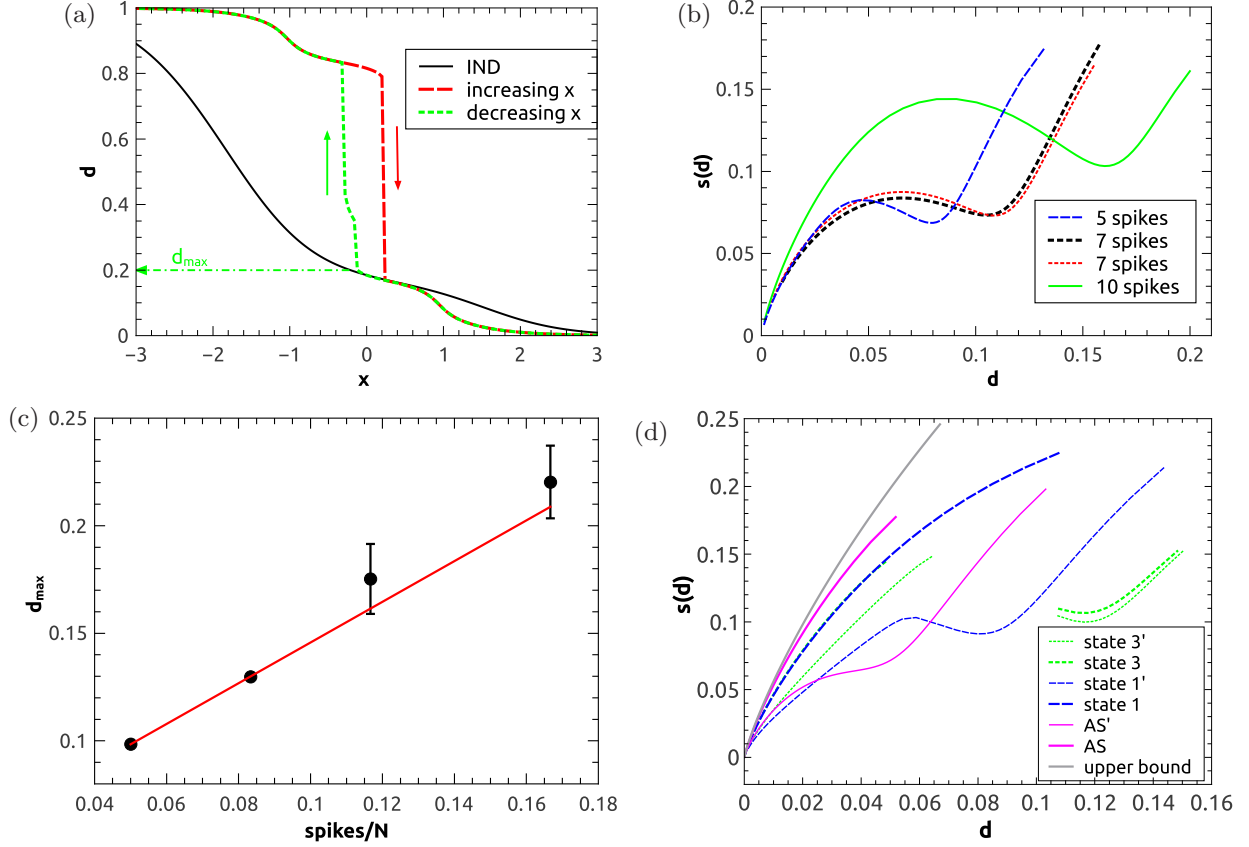


FIG. 3. Code word organization of the neural data ( $N = 60$ ). (a) A first-order phase transition in Hamming distance when the coupling field is tuned. The reference is a code word of ten spike-counts. The neural code-word space structure is shaped by the correlations in the neural spiking activity. The first-order transition disappears for independent model (IND).  $d_{\max}$  defines the distance at which the low- $d$  branch in the hysteresis loop terminates. (b) Distance-dependent entropy landscape from reference neural code words of different spike-counts. (c) Maximum distance  $d_{\max}$  versus spike-counts of the reference states (distance from AS state). Five references for each spike-count are randomly chosen. The line is a linear fit. (d) Distance entropy from neural code words (state  $a'$ ) and their corresponding LEM (state  $a$ ). The corresponding LEM are identified by GDD. The random code word limit is the upper bound.

corresponding LEM codeword. Moreover, for some states (e.g., 3 and 3'), there exist two continuous parts separated by a gap in the distance entropy curve. We shall elaborate this phenomenon in the following section by studying a larger population, where the effect becomes much more evident. This shows another clear evidence for the clustering of neural code words.

#### D. More complicated structure observed for large neural populations

The property of the neural codeword shown above is still preserved when large populations of neurons are considered. In Fig. 7, we show the theoretical result computed on a network sample of  $N = 100$ . As the network size grows, the number of LEM detected by GDD method also increases. Accordingly, the internal structure of the code words becomes more complicated [a rough visualization is given by the MDS map, see Fig. 6(b)]. As shown in Fig. 7(a), there exist two hysteresis loops separated by another monostable branch (two curves for increasing and decreasing  $x$  coincide with each other). These two successive hysteresis loops naturally arise if there exist three deep minima in the energy landscape, where

sweeping  $x$  shifts a dominant contribution from one to another. Fig. 7(b) shows that  $d_{\max}$  grows with spike-counts (distance from the AS state). The growth is likely nonlinear in this case, perhaps induced by the complexity of the state space. The fraction of neural code words that can reach the AS state without in-between gaps reduces from the result of the previous section to about 76.05%. Note that this number is still dominant compared to the reachability of other detected LEM. Again, the AS state has the densest surrounding core, characterized by the rapid growth of the entropy with distance [Fig. 7(c)]. The entropy landscape surrounding the AS state does not have a second monostable branch beyond the first entropy gap, except at a biologically implausible distance close to 1. This might be because there is no deep enough minima around the AS state. In contrast, the entropy landscape surrounding some other reference code words, e.g., state 1', exhibits a second monostable branch beyond the first entropy gap [see Fig. 7(a)], likely indicating that there is another deep minimum around them.

To demonstrate the implication of the entropy landscape, we study how distance from a local energy minimum changes with time when the neural system explores the state space. We use the local dynamics rule characterized by the transition probability  $w(\sigma_i \rightarrow -\sigma_i | H_i) = e^{-2\sigma_i H_i}$ , where

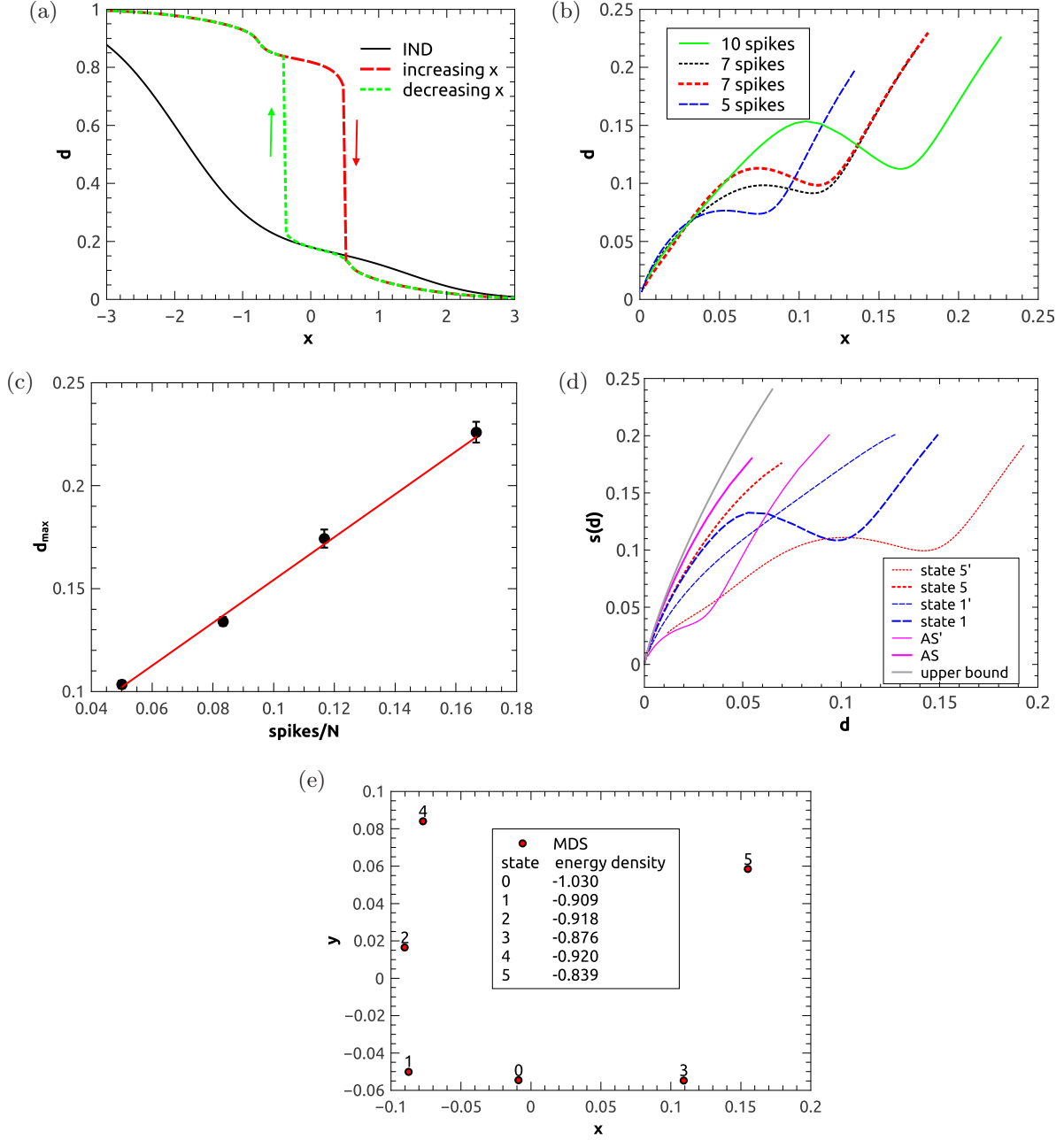


FIG. 4. Entropy landscape of the neural data ( $N = 60$ , another typical example). (a) A first-order phase transition in Hamming distance when the coupling field is tuned. The transition disappears for an independent model (IND). (b) Distance entropy from reference neural code words of different spike-counts. (c) Maximum distance  $d_{\max}$  at which the low- $d$  branch in the hysteresis loop terminates versus spike-counts of the reference (distance from AS state). Five references for each spike-count are considered. The line is a linear fit (slope= $1.041 \pm 0.040$ ). (d) Distance entropy from neural code words and their corresponding LEM. (e) Low-dimensional representation of LEM corresponding to (d) by multidimensional scaling (MDS) analysis ( $y, x$  serve as coordinates). State 0 is the AS state.

$H_i = h_i + \sum_j J_{ij} \sigma_j$  denotes the effective spiking bias of neuron  $i$ . Under this dynamics, states are sampled from the original distribution  $P(\sigma) \propto \exp(-\beta E(\sigma))$ . Note that the GDD rule to obtain LEM allows only monotonically decreasing energy on the energy surface. In contrast, the current dynamics rule allows the energy to increase occasionally. Sampled distance from a reference local energy minimum  $\sigma^*$  is denoted by  $d_0(t) = (1 - \sigma^T(t) \sigma^*/N)/2$  where  $t$  denotes the time step. The mean field prediction  $d_0^{\text{MF}}$  of a typical code-word distance is given by setting  $x = 0$  and initializing the iteration equation

(see the Appendix) at  $\sigma^*$ . Note that  $x = 0$  corresponds to the case without distance-constraint, and thus takes into account all code words in the cluster that  $\sigma^*$  belongs to. As expected, this calculation predicts the fluctuation plateau of  $d_0(t)$  close to the reference, as shown in Figs. 8(a) and 8(b). Note that the local dynamics escapes fast from the AS state [see the inset of Fig. 8(a)], which may be related to its very small core [Fig. 7(c)]. The same qualitative behavior holds for the smaller network ( $N = 60$ , see Fig. 9) and when the neural dynamics is simulated starting from a non-LEM code word.



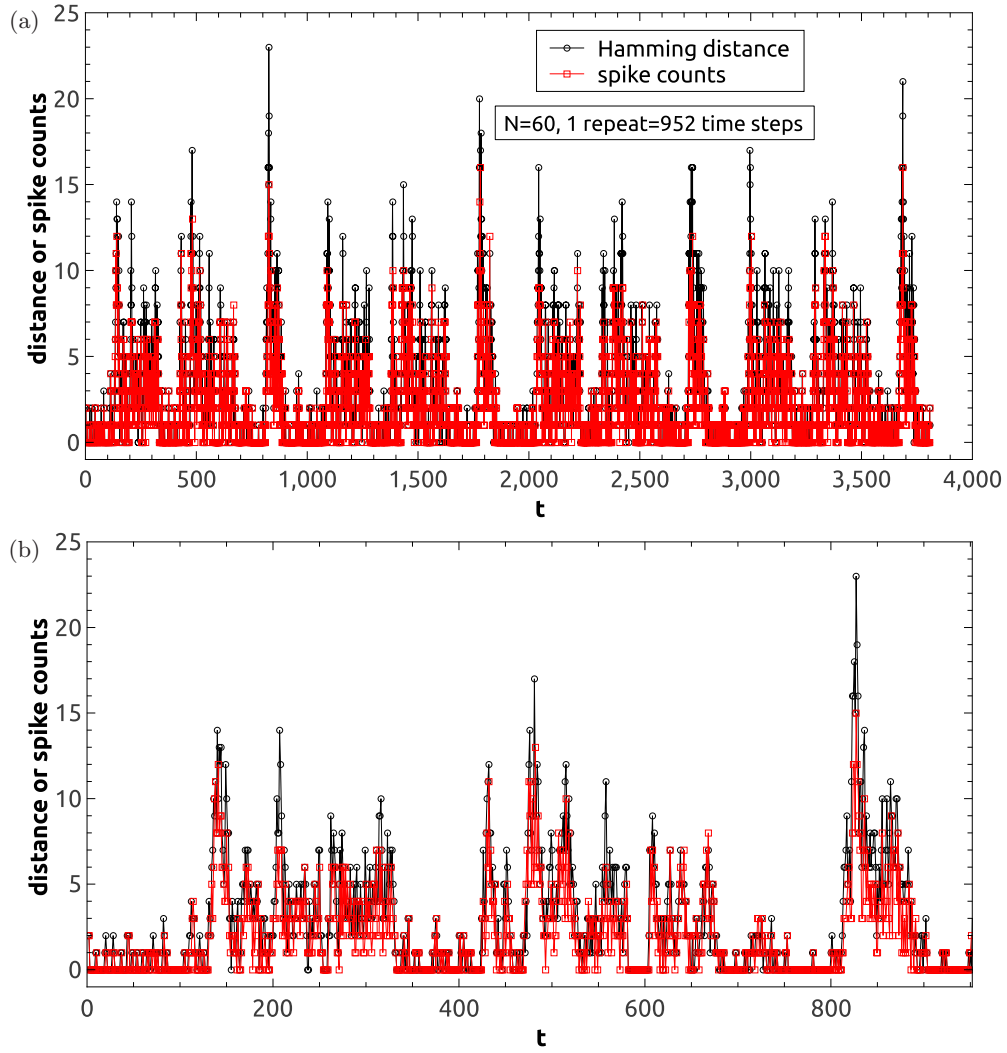


FIG. 5. Distance or spike-counts evolution of the neural data ( $N = 60$ , typical example shown in Fig. 3). The time-dependent Hamming distance is defined as  $d(t) \equiv \frac{N - \sum_i \sigma_i(t)\sigma_i(t+1)}{2}$ , and the time-dependent spike-counts  $r(t) \equiv \sum_i \delta(\sigma_i(t) - 1)$ . (a) The profile for four repeats. Trial-to-trial variability is observed. (b) The profile for only one repeat. The AS state is frequently visited, and the neural network seems to explore the state space by local moves.

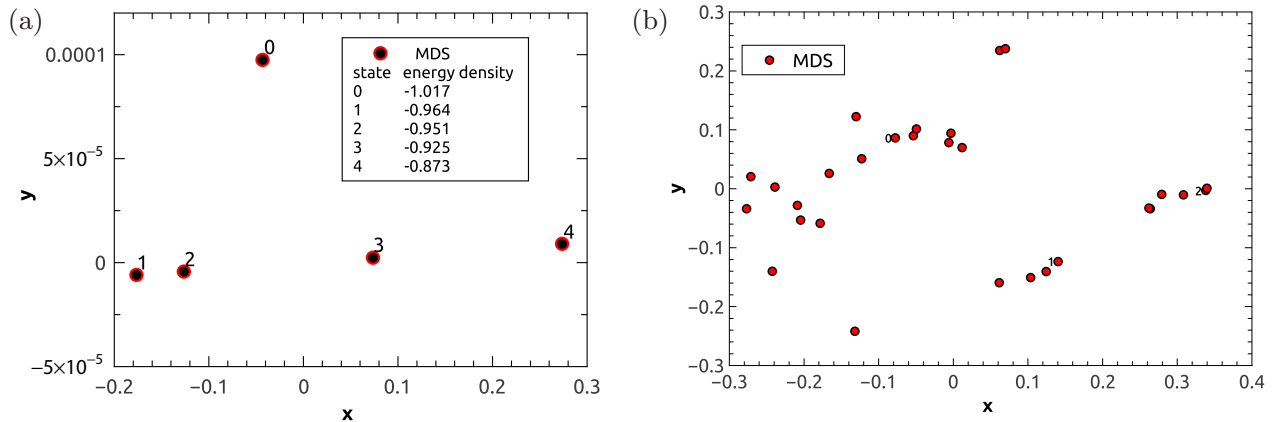


FIG. 6. Low-dimensional representation of LEM (identified by GDD) by multidimensional scaling (MDS) analysis ( $y, x$  serve as coordinates). State 0 is the AS state. (a) MDS map for a population of 60 neurons (see Fig. 3). (b) MDS map for a population of 100 neurons (see Fig. 7), in which 29 LEM are identified by GDD method. It becomes difficult to represent faithfully these LEM in a low-dimensional space (some information are lost), nevertheless, the map still shows how they are distributed.

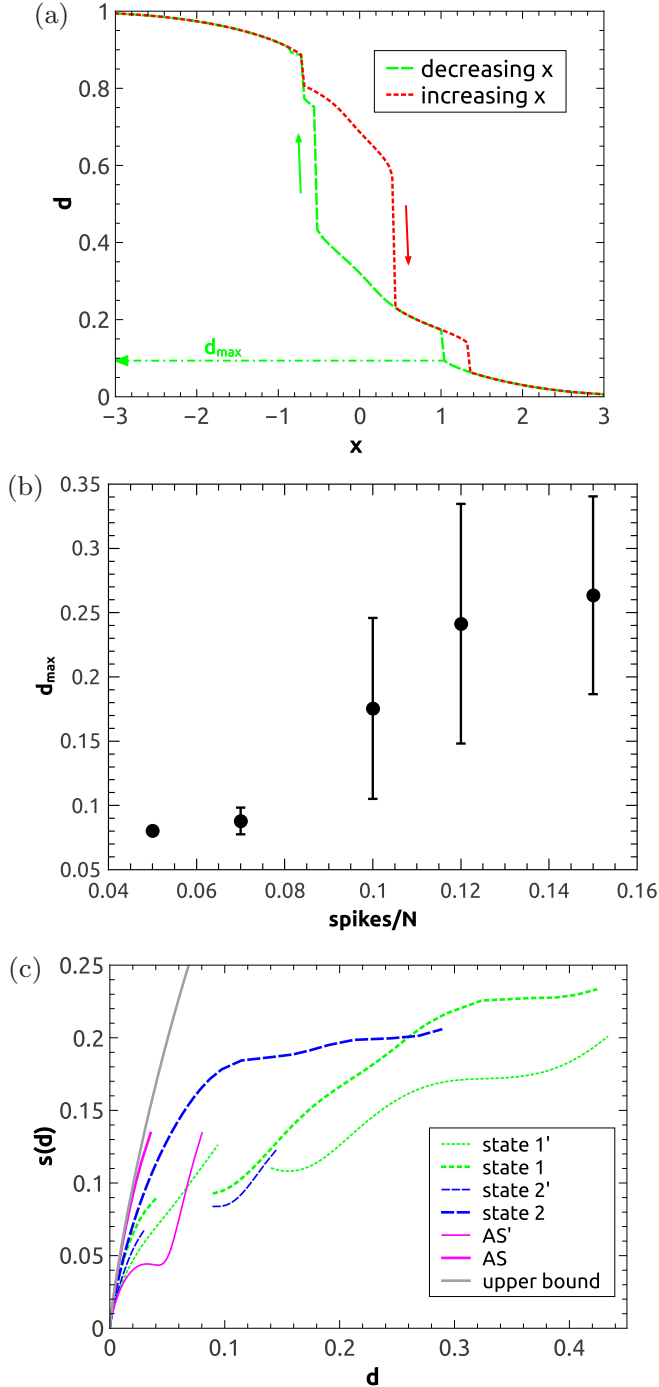


FIG. 7. Code word organization of the neural data ( $N = 100$ ). (a) Two hysteresis loops are observed. The reference is state 1' [see (c)]. (b) Maximum distance  $d_{\max}$  at which the low- $d$  branch in the hysteresis loop terminates versus spike-counts of the reference (distance from AS state). Five references for each spike-count are randomly chosen. (c) Entropy curve for different code words and their assigned LEM. Complex structure is observed for state 1, 1', and 2'.

### III. DISCUSSION

In this work, we have established the resemblance of code word organization between the retinal network and the

Hopfield network. In previous studies, the memory retrieval function of Hopfield network was empirically compared to the behavior of real networks [8,10,16,19]. However, no theoretical framework was proposed to build a solid relationship between these artificial and real biological networks. In fact, they are naturally distinct in terms of detailed parameters. Surprisingly, we have found that the two networks both similarly organize their code words. The clustering of codewords has been identified by the first-order phase transition in the code-word distance. This transition is accompanied by hysteresis loops, which becomes increasingly complex as the network size grows. We have also revealed that the AS state has a distinct role from other codewords. The number of code words surrounding the AS state always grows much more rapidly as a function of distance compared to that surrounding other code words. Interestingly, despite the presence of entropy gaps, most codewords even far away from the AS state could still have easy access to it because of their surrounding dense cores of code words typically extending beyond the AS state. Thus, the most frequently observed AS state plays a key role in serving as a hub facilitating neural exploration of the code-word space.

The only knowledge a neuronal population can have comes from the population activity of interacting neurons. As shown in our study, there exists well-designed structure of code words in the neural state space. The code words are partitioned into multiple clusters separated by entropy gaps. Moreover, this emergent property remains even if one-fourth of our data is used to learn the model (see Fig. 10). Thus the revealed organization structure is most likely an intrinsic property of the retinal network, and downstream brain areas may benefit from this structure for decoding purpose.

The clustering is functionally advantageous and intimately related to the network function, i.e., pattern completion (error-correction) and pattern separation (discrimination ability). Upon repeated presentations of the same visual stimulus, the neural responses show strong trial-to-trial variability [10]. However, all code words belonging to the same core perhaps encode the same feature of the semantic information [19]. This property also allows the neural code to be robust against the ubiquitous noise in nervous systems [20]. In an analogous way to error-correcting codes [21,22], even if the neural code word is corrupted by a small amount of noise, the dense core structure still allows population coding of stimulus features. Therefore, the non-trivial internal structure of the neural code-word space is useful for the neural population not only to discriminate different neural activity patterns, but also to carry out error-correction [23,24].

The retina as an early visual system should adapt to the visual stimulus distribution to efficiently transmit relevant information to downstream brain areas. The energy landscape shaped by the neural interactions likely depends on the natural scene statistics [25]. It is therefore interesting to study their relationship under the current context.

The code-word space structure quantitatively predicts the fluctuation plateau of the simulated neural dynamics starting from LEM. Hence, our analytic framework establishes the relationship between the simulated neural dynamics and clustering of code words. In previous studies, the match between spontaneous neural activity and the stimulus-evoked

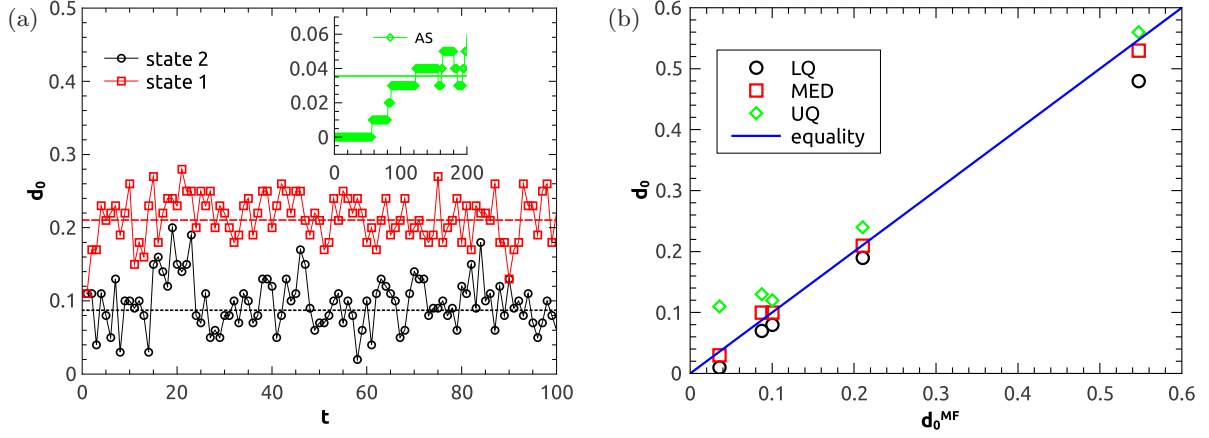


FIG. 8. Mean field theory predicts the plateau of the distance dynamics starting from LEM [ $d_0(t)$ ]. (a) Typical trajectory observed for reference AS (inset), states 1 and 2 in simulations. The (solid, dashed, dotted) line is the theoretical prediction computed at  $x = 0$  for each reference. (b) The fluctuation plateau of  $d_0(t)$  is predicted by the mean field theory ( $d_0^{MF}$ ). Five trials from the same reference are considered for each data point. Each trial lasts for 100 steps. Each step corresponds to  $N$  proposed flips. Note that in the inset of (a), one step corresponds to one possible flip. LQ: lower quartile; MED: median; UQ: upper quartile.

activity increases during development especially for natural stimuli [26], and the spontaneous activity outlines the regime of evoked neural responses [27]. Our analysis might further

reveal how spontaneous neural activity is related to the vocabulary of neural code words a neural circuit learns to internally represent external worlds.

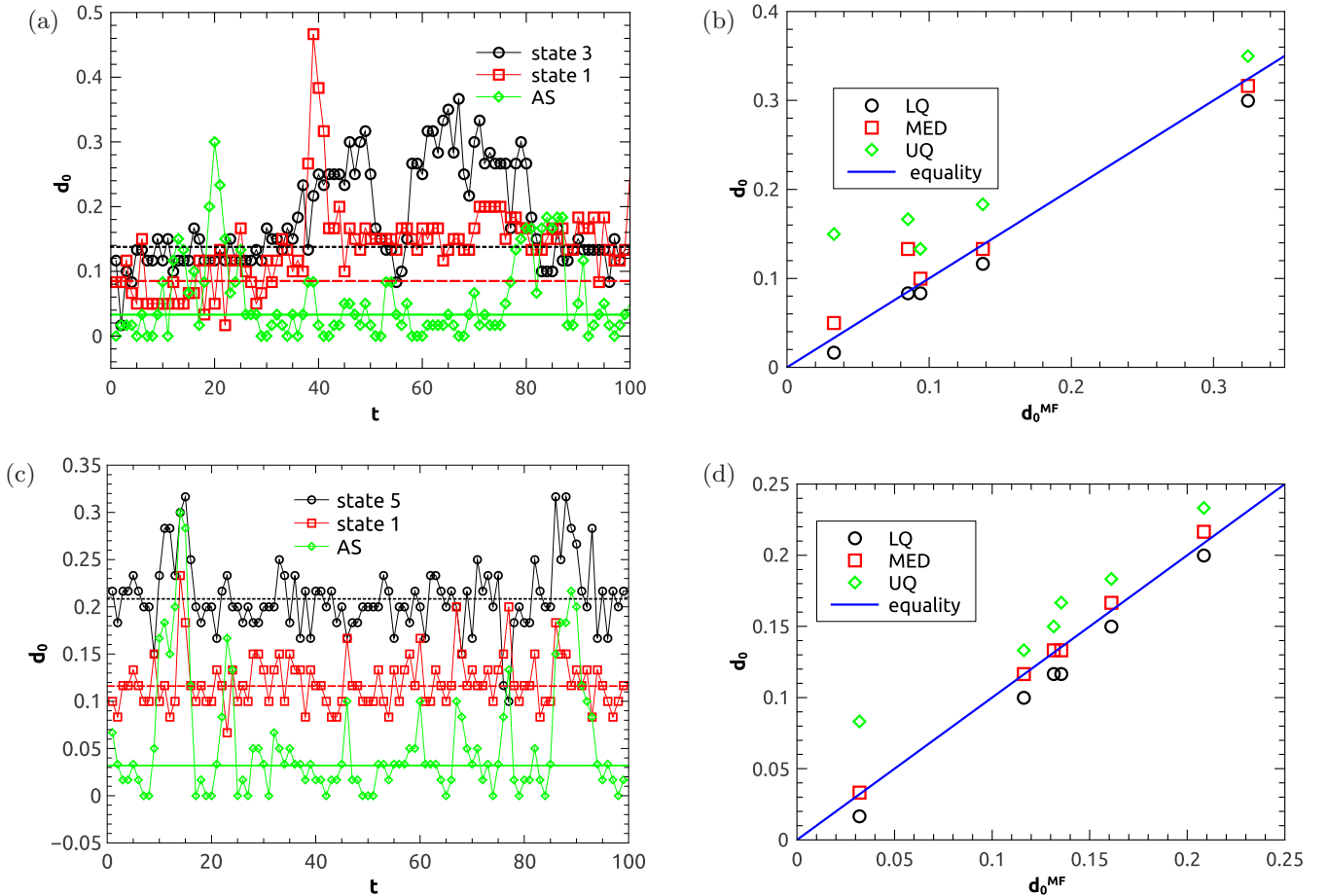


FIG. 9. Neural dynamics starting from LEM ( $d_0(t)$ ). (a,b) the network with 60 neurons in the Fig. 3. (c,d) the network with 60 neurons corresponding to Fig. 4. (a,c) typical trajectory observed in simulations. The (solid, dashed, dotted) line is the theoretical prediction computed at  $x = 0$  for each reference. (b,d) the fluctuation plateau of  $d_0(t)$  is predicted by the mean field theory ( $d_0^{MF}$ ). Five trials from the same reference are considered for each data point. Each trial lasts for 100 steps. LQ: lower quartile; MED: median; UQ: upper quartile.



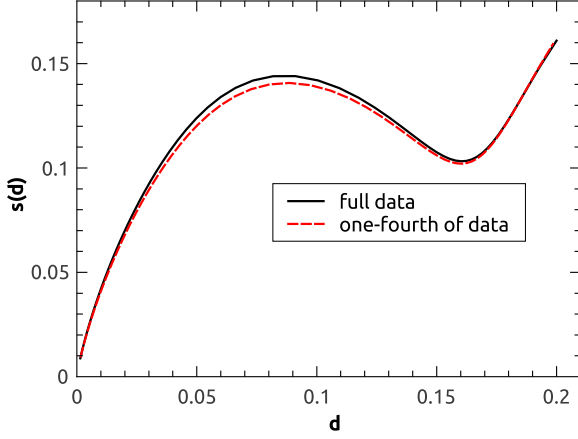


FIG. 10. Entropy landscape for  $N = 60$ . The same reference codeword has ten spikes but two data of different lengths are learned. The problem structure is not affected by the finite sampling of the data.

Overall, our study provides an important step to understand the stationary distribution of neural spiking patterns and its functional relevance, which also sheds light on future studies of the sensory processing in other brain areas.

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#### APPENDIX: METHODS

##### 1. Simultaneous recordings of neural activity in populations of retinal ganglion cells

The spiking activity of 160 retinal ganglion cells was collected from a  $450 \times 450 \mu\text{m}$  patch of the salamander retina, when a repeated naturalistic movie was presented. The visual stimulus consists of 297 repeats of a 19s long movie clip being a gray movie of swimming fish and swaying water plants in a tank (data courtesy of Michael J. Berry II, see experimental details in the original paper [10,17]). The spike train data are binned with the bin size  $\tau = 20$  ms reflecting the temporal correlation time scale, yielding about  $280 \times 10^3$  binary neural codewords for model analysis.

##### 2. Maximum entropy model

For a neuronal population of size  $N$ , the neural spike trains of duration  $T$  are binned at temporal resolution  $\tau$ , producing  $M = \lceil T/\tau \rceil$  samples of  $N$ -dimensional binary neural code words. We use  $\sigma_i = +1$  to indicate spiking activity of neuron  $i$ , and  $\sigma_i = -1$  for silent activity. The neural responses to repeated stimulus are highly variable (so-called trial-to-trial variability, see Fig. 5). To model the neural code-word statistics, we assign each code word  $\sigma$  a cost function (energy in statistical physics jargon)  $E(\sigma)$ , then the probability of observ-

ing one code word  $\sigma$  is written as  $P(\sigma) \propto \exp(-E(\sigma))$ , where

$$E(\sigma) = - \sum_i h_i \sigma_i - \sum_{i < j} J_{ij} \sigma_i \sigma_j. \quad (\text{A1})$$

The spiking bias  $h_i$  and neuronal coupling  $J_{ij}$  are constructed from the spike train data such that the spiking rate  $m_i$  and the pairwise correlation  $C_{ij}$  under the model match those computed from the data. High energy state  $\sigma$  corresponds to low probability of observation. This is a low-dimensional representation of the original high-dimensional neural code words, since we need only  $N + N(N-1)/2$  model parameters.

To find the model parameters, we apply the maximum likelihood learning principle corresponding to maximizing the log-likelihood  $P(\sigma)$  with respect to the parameters. The learning equation is given by

$$h_i^{t+1} = h_i^t + \eta(\langle \sigma_i \rangle_{\text{data}} - \langle \sigma_i \rangle_{\text{model}}), \quad (\text{A2a})$$

$$J_{ij}^{t+1} = J_{ij}^t + \eta(\langle \sigma_i \sigma_j \rangle_{\text{data}} - \langle \sigma_i \sigma_j \rangle_{\text{model}}), \quad (\text{A2b})$$

where  $t$  and  $\eta$  denote the learning step and learning rate, respectively. The maximum likelihood learning shown here has a simple interpretation of minimizing the Kullback-Leibler divergence between the empirical probability and the model probability [28,29]. In the learning equation [Eq. (A2)], the data dependent terms can be easily computed from the binned neural data. However, the model expectation of the spiking rate (magnetization in statistical physics) and pairwise correlation is quite hard to evaluate without any approximations. Here we propose the mean field method to tackle this difficulty.

The statistical properties of the model [Eq. (A1)] can be analyzed by the cavity method in the mean field theory [30]. The self-consistent equations are written in the form of message passing (detailed derivation is given in Refs. [15,22]) as

$$m_{i \rightarrow a} = \tanh \left( h_i + \sum_{b \in \partial i \setminus a} \tanh^{-1} \hat{m}_{b \rightarrow i} \right), \quad (\text{A3a})$$

$$\hat{m}_{b \rightarrow i} = \tanh \Gamma_b \prod_{j \in \partial b \setminus i} m_{j \rightarrow b}, \quad (\text{A3b})$$

where  $\partial b \setminus i$  denotes the member of interaction  $b$  except  $i$ , and  $\partial i \setminus a$  denotes the interaction set  $i$  is involved in with  $a$  removed.  $\Gamma_a \equiv J_{ij}$  and  $a \equiv (ij)$ .  $m_{i \rightarrow a}$  is interpreted as the message passing from the neuron  $i$  to the interaction  $a$  it participates in, while  $\hat{m}_{b \rightarrow i}$  is interpreted as the message passing from the interaction  $b$  to its member  $i$ . Iteration of the message passing equation on the inferred model would converge to a fixed point corresponding to a global (local) minimum of the free energy (in the cavity method approximation [15])

$$F \equiv -\ln Z = - \sum_i \ln Z_i + \sum_a (|\partial a| - 1) \ln Z_a, \quad (\text{A4})$$

where  $Z$  is the normalization constant (partition function) of the model probability  $P(\sigma)$ . The free energy contribution of one neuron is  $-\ln Z_i = -\ln \sum_{x=\pm 1} \mathcal{H}_i(x)$ , where  $\mathcal{H}_i(x) \equiv e^{x h_i} \prod_{b \in \partial i} \cosh \Gamma_b (1 + x \hat{m}_{b \rightarrow i})$ , and the free energy contribution of one interaction is  $-\ln Z_a = -\ln \cosh \Gamma_a - \ln (1 + \tanh \Gamma_a \prod_{i \in \partial a} m_{i \rightarrow a})$ . At the same time, the model

spiking rate and multi-neuron correlation can also be estimated as

$$m_i = \tanh \left( h_i + \sum_{b \in \partial i} \tanh^{-1} \hat{m}_{b \rightarrow i} \right), \quad (\text{A5a})$$

$$C_a = \frac{\tanh \Gamma_a + \prod_{i \in \partial a} m_{i \rightarrow a}}{1 + \tanh \Gamma_a \prod_{i \in \partial a} m_{i \rightarrow a}}. \quad (\text{A5b})$$

We have defined  $m_i = \langle \sigma_i \rangle$  and  $C_a = \langle \prod_{i \in \partial a} \sigma_i \rangle$ . Note that the iteration converges in a few steps at each learning stage, and estimated magnetizations as well as correlations are used in the gradient ascent learning step. Here the multi-neuron correlation is calculated directly from the cavity method approximation [31] and expected to be accurate enough for current neural data analysis. Another advantage is the low computational cost. A more accurate expression could be derived from linear response theory [32] with much more expensive computational cost.

Finally, one can also estimate the entropy of the model from the fixed point of the message passing equation. The entropy is defined as  $S = -\sum_{\sigma} P(\sigma) \ln P(\sigma)$ , and it measures the capacity of the neural population for information transmission. More obvious variability of the neural responses implies larger entropy value. Based on the standard thermodynamic relation,  $S = -F + E$ , where  $E$  is the energy of the neural population and given by

$$E = -\sum_i \Delta E_i + \sum_a (|\partial a| - 1) \Delta E_a, \quad (\text{A6a})$$

$$\Delta E_i = \frac{h_i \sum_{x=\pm 1} x \mathcal{H}_i(x) + \sum_{x=\pm 1} \mathcal{G}_i(x)}{\sum_{x=\pm 1} \mathcal{H}_i(x)}, \quad (\text{A6b})$$

$$\Delta E_a = \Gamma_a \frac{\tanh \Gamma_a + \prod_{i \in \partial a} m_{i \rightarrow a}}{1 + \tanh \Gamma_a \prod_{i \in \partial a} m_{i \rightarrow a}}, \quad (\text{A6c})$$

$$\begin{aligned} \mathcal{G}_i(x) = \sum_{b \in \partial i} e^{x h_i} & \left[ \Gamma_b \sinh \Gamma_b (1 + x \hat{m}_{b \rightarrow i}) \right. \\ & \left. + x \Gamma_b \cosh \Gamma_b (1 - \tanh^2 \Gamma_b) \prod_{j \in \partial b \setminus i} m_{j \rightarrow b} \right] \\ & \times \prod_{a \in \partial i \setminus b} \cosh \Gamma_a (1 + x \hat{m}_{a \rightarrow i}). \end{aligned} \quad (\text{A6d})$$

### 3. Distance-constrained entropy analysis

To uncover the internal structure of the neural code-word space, we introduce a modified probability measure [14]

$$P(\sigma) = \frac{1}{Z} \exp \left( \sum_i \beta h_i \sigma_i + \sum_{i < j} \beta J_{ij} \sigma_i \sigma_j + x \sum_i \sigma_i^* \sigma_i \right), \quad (\text{A7})$$

where  $\beta$  is the inverse temperature or neural reliability, and the coupling field  $x$  is introduced to control the overlap between the neural code word  $\sigma$  and a reference one  $\sigma^*$ .

The partition function  $Z$  can be approximated by a saddle point analysis, i.e.,  $Z \simeq \exp(Ns(d, \epsilon) - \beta N\epsilon + x Nq)$ , from

which the free energy per neuron  $f$  (density) is given by  $-\beta f = s(d, \epsilon) - \beta \epsilon + xq$ , where  $\epsilon$  is the energy density ( $E/N$ ),  $s(d, \epsilon)$  the entropy density ( $S/N$ ) and  $q$  the typical value of the overlap ( $\sigma^T \sigma^*/N$ ). Note that the Hamming distance per neuron is related to the overlap by  $d = (1 - q)/2$ . According to the double Legendre transform, the entropy density is calculated via  $s(d, \epsilon) = -\beta f + \beta \epsilon - xq$ .  $e^{Ns(d, \epsilon)}$  counts the number of valid configurations around the reference satisfying both the distance constraint ( $d$ ) and the energy density ( $\epsilon$ ). Here  $\beta$  controls the energy level and  $x$  selects the overlap or Hamming distance. The overlap  $q$  is given by  $q = \frac{1}{N} \sum_i \sigma_i^* m_i$  with  $m_i$  being calculated under the modified probability measure.  $(x, \beta)$  obeys the following equations:  $\partial s(d, \epsilon)/\partial d = 2x$  and  $\partial s(d, \epsilon)/\partial \epsilon = \beta$ . In this setting, the above iteration equations [Eq. (A3)] remain unchanged except that the bias is changed to  $h_i \rightarrow \beta h_i + x \sigma_i^*$  and the coupling is rescaled as  $J_{ij} \rightarrow \beta J_{ij}$ . For the real neuronal network, the neural reliability  $\beta = 1$ , since the constructed biases and couplings reflect the neural noise observed in the spike train data. For the Hopfield model, higher  $\beta$  implies weaker thermal fluctuation and may correspond to a retrieval phase for pattern completion.

Note that to compute the entropy curve for metastable or unstable branches of distance-coupling field curve, one has to fix  $d$  by searching for compatible coupling field  $x$ , e.g., by the secant method [33].

### 4. Finding local energy minima from neural activity pattern

To search for a local energy minimum starting from any given neural activity pattern, we use greedy descent dynamics (GDD) in the energy landscape [10]. To be more precise, for each neuron, we flip its activity if the flip will decrease the energy. If we could not decrease the energy by flipping any neuron's activity, then a local energy minimum is identified. Such minima are also called single-flip stable attractors, i.e., their energy cannot be decreased by flipping any single neuron's activity. We choose randomly a pattern set of size 2000 from the neural data to ensure that any two patterns are rarely identical. By applying the GDD method, we identify a LEM set whose size is much smaller than that of the pattern set, with a large portion of patterns evolving to the all-silent state. The number of LEM increases with the network size. These LEM are then expressed in a low-dimensional space (called multidimensional scaling analysis (MDS) [34]). MDS represents the proximity between LEM in the high dimensional space with some degree of fidelity by the distance between points in the low dimensional space.

### 5. Independent maximum entropy model

In the case of fitting only the first moments (mean spiking activity), the distance entropy can be computed exactly. The result is given by

$$\begin{aligned} s(q(x)) = \frac{1}{N} \sum_i \ln 2 \cosh(h_i + x \sigma_i^*) \\ - \frac{1}{N} \sum_i (h_i + x \sigma_i^*) \tanh(h_i + x \sigma_i^*), \end{aligned} \quad (\text{A8})$$

where  $h_i = \frac{1}{2} \ln \frac{1+m_i}{1-m_i}$  and  $q(x) = \frac{1}{N} \sum_i \sigma_i^* \tanh(h_i + x \sigma_i^*)$ .

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