Spike Triggered Covariance in Strongly Correlated Gaussian Stimuli

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Abstract

Many biological systems perform computations on inputs that have very large dimensionality. Determining the relevant input combinations for a particular computation is often key to understanding its function. A common way to find the relevant input dimensions is to examine the difference in variance between the input distribution and the distribution of inputs associated with certain outputs. In systems neuroscience, the corresponding method is known as spike-triggered covariance (STC). This method has been highly successful in characterizing relevant input dimensions for neurons in a variety of sensory systems. So far, most studies used the STC method with weakly correlated Gaussian inputs. However, it is also important to use this method with inputs that have long range correlations typical of the natural sensory environment. In such cases, the stimulus covariance matrix has one (or more) outstanding eigenvalues that cannot be easily equalized because of sampling variability. Such outstanding modes interfere with analyses of statistical significance of candidate input dimensions that modulate neuronal outputs. In many cases, these modes obscure the significant dimensions. We show that the sensitivity of the STC method in the regime of strongly correlated inputs can be improved by an order of magnitude or more. This can be done by evaluating the significance of dimensions in the subspace orthogonal to the outstanding mode(s). Analyzing the responses of retinal ganglion cells probed with 1/² Gaussian noise, we find that taking into account outstanding modes is crucial for recovering relevant input dimensions for these neurons.

Introduction

How do neurons encode sensory stimuli? One of the primary difficulties in answering this long-standing problem is the fact that sensory stimuli have high dimensionality. For example, responses of many visual neurons are affected by image patterns that require at least a 10 × 10 pixel grid for their description as well as a temporal history spanning multiple time bins or basis functions. Determining what input combinations affect the neural responses is a key step in characterizing the neural computation. Broadly speaking, to detect the presence of certain features in the environment over a range of distances and light conditions, one needs to disambiguate the presence of this feature at a weak contrast from the presence of a similar, but different feature presented at a higher contrast. This can only be achieved with nonlinear functions that depend on multiple input components, such as the presence of an edge of correct orientation and the absence of the edge orthogonal to it [1]. In support of these arguments, the responses of neurons in different sensory modalities are found to be sensitive to multiple input combinations. Examples include vision [2–7], audition [8–10], olfaction [11], somatosensation [12] and mechanosensation [13]. Neurons respond with all-or-none responses termed spikes. The goal of different methods for characterizing neural feature selectivity is to determine how the probability of eliciting a spike from a neuron depends on its inputs. The underlying assumption is that this dependence of spike probability on input parameters will have a low-dimensional structure. Finding either the linear input dimensions that modulate the spike probability (we will refer to these dimensions as relevant) or quadratic forms of inputs [14–16] is the focus of much of the current research in the field.

Much of the analysis of neural selectivity for multiple input combinations has been carried out using uncorrelated (“white noise”) or weakly correlated inputs. With such inputs, the relevant input dimensions can be found using a computationally inexpensive method known as spike-triggered covariance (STC) [6,7,17–22]. The STC method works by comparing the change in variance along different dimensions in the input space across all stimuli and across stimuli that elicited a spike. The dimensions along which the variance is found to be significantly different represent the relevant input dimensions for the response of a particular neuron. The method is not limited to strictly Gaussian inputs provided that the inputs are still circularly symmetric [23], which is another example of an input distribution without correlations.
Author Summary

In many areas of computational biology, including the analyses of genetic mutations, protein stability and neural coding, as well as in economics, one of the most basic and important steps of data analysis is to find the relevant input dimensions for a particular task. In neural coding problems, the spike-triggered covariance (STC) method identifies relevant input dimensions by comparing the variance of the input distribution along different dimensions to the variance of inputs that elicited a neural response. While in theory the method can be applied to Gaussian stimuli with or without correlations, it has so far been used in studies with only weakly correlated stimuli. Here we show that to use STC with strongly correlated, 1/f-type inputs, one has to take into account that the covariance matrix of random samples from this distribution has a complex structure, with one or more outstanding modes. We use simulations on model neurons as well as an analysis of the responses of retinal neurons to demonstrate that taking the presence of these outstanding modes into account improves the sensitivity of the STC method by more than an order of magnitude.

Spike Triggered Covariance in Correlated Stimuli

In principle the STC method can also be used with correlated Gaussian stimuli [7,20]. The case of correlated stimuli - especially with strong correlations, where the second moment of the covariance spectrum may be infinite - is important for neural coding. This is because signals in the sensory environment possess such correlations in both the second and higher orders [24–30]. Because the properties of a cell’s relevant subspace may change depending on the stimulus statistics as a result of adaptation [31,32], it may not be sufficient to study neural coding using uncorrelated stimuli. Here we show that with strongly correlated inputs, the significance analysis for determining which of the dimensions obtained by the STC method are relevant for neural spiking needs to be modified to take into account a rather complicated covariance structure of randomly selected inputs drawn from such input ensembles. The nonuniform covariance structure, which has properties akin to the graph laplacian in small-world networks [33], breaks the symmetry in the input space, and therefore may obscure many significant dimensions.

The most prominent aspect of the natural scenes covariance structure is the presence of the so-called “coherent” mode [34]. This stimulus dimension approximately corresponds to the zero frequency input component and has a corresponding eigenvalue that is at least 10 times larger than the mean eigenvalue of the input covariance matrix. Even in datasets of fairly large size, the extremely large variance along the coherent mode obscures many of the truly relevant dimensions for neural spiking (Fig. 1). These effects are also reproduced in our analysis of the responses of ganglion cells from the salamander retina probed with 1/f-type naturalistic Gaussian stimuli. We identify a close relationship between the covariance structure derived from natural scenes to that defined by the Spiked-Wishart matrix model [35,36]. This allows us to explain the effects in the context of the STC method using results from random matrix theory, and suggest ways to bypass sampling variability along the outstanding modes.

Results

Spike triggered covariance

Mathematically, the first step in the STC method is to compute the covariance matrix of stimuli that lead to a spike $C_{\text{spike}}$ and the covariance matrix of all stimuli $C_{\text{stim}}$:

\[
C_{\text{spike}} = \frac{1}{N_{\text{spike}} - 1} \sum_{i=1}^{N_{\text{spike}}} (\mathbf{s}'_i - \langle \mathbf{s}'_i \rangle_{\text{spike}})(\mathbf{s}'_i - \langle \mathbf{s}'_i \rangle_{\text{spike}}) \tag{1}
\]

\[
C_{\text{stim}} = \frac{1}{N - 1} \sum_{i=1}^{N} (\mathbf{s}'_i - \mathbf{s}_i)(\mathbf{s}'_i - \mathbf{s}_i). \tag{2}
\]

Here, $N_{\text{spike}}$ is the number of recorded spikes, $N$ is the number of stimulus frames, $\mathbf{s}'_i$ is the value of the stimulus along the $i$th dimension at time $t$, the $\langle \cdot \rangle$ denotes the average across the input distribution and $\langle \mathbf{s}'_i \rangle_{\text{spike}}$ is the average across the distribution of inputs that triggered a spike (the so called “spike-triggered-average”).

As the second step, one computes the difference between these covariance matrices:

\[
\Delta C = C_{\text{spike}} - C_{\text{stim}}, \tag{3}
\]

and finds the eigenvalues that are significantly different from zero. The corresponding eigenvectors span the neuron’s relevant subspace.

To determine statistical significance of the eigenvalues, they need to be compared to the null distribution, which is the distribution of eigenvalues of the matrices $\Delta C_{\text{null}} = C_{\text{null}} - C_{\text{stim}}$. The matrices $\Delta C_{\text{null}}, C_{\text{null}}$ are formed assuming no association between the stimulus and the neural response, i.e. by using random spike times chosen at the same rate found for real neurons. If the spike train has particular temporal structure (e.g. bursting, a refractory period), the $C_{\text{null}}$ is obtained by random shifts of the spike train with periodic boundary conditions [20]. Significant eigenvalues of $\Delta C$ can be positive or negative. The procedures for determining statistical significance are detailed in Materials and Methods.

The final step of the STC method is to remove stimulus correlations from the estimate of dimensions found to be significant. This can be done by multiplying them with the (pseudo)inverse of $C_{\text{stim}}$ [see Materials and Methods]. The method which we use to find the optimal rank of the pseudoinverse matrix is detailed in [22,37] and for completeness described in Materials and Methods.

We note that this approach, Eqs. (1)–(3), of finding the relevant stimulus dimensions by diagonalizing $\Delta C$ is equivalent to seeking eigenvectors of the following matrix [20]:

\[
\Delta \mathbf{C}_{ij} = \frac{1}{N_{\text{spike}} - 1} \sum_{i=1}^{N_{\text{spike}}} (\mathbf{s}'_i - \mathbf{s}_i)(\mathbf{s}'_i - \mathbf{s}_i) - \frac{1}{N - 1} \sum_{i=1}^{N} (\mathbf{s}'_i - \mathbf{s}_i)(\mathbf{s}'_i - \mathbf{s}_i). \tag{4}
\]

This matrix describes a change in the second moment between the distributions stimuli that elicit a spike and that of all stimuli, after subtracting the mean stimulus $\bar{s}$. Despite the fact that $\Delta C \neq \Delta \mathbf{C}$, their eigenvectors coincide.

In another formulation, instead of subtracting the matrix $C_{\text{stim}}$ in Eq. (3), the stimulus is decorrelated (“whitened”) prior to its spike triggered characterization [7]. For completeness, the details of this method are brought in Materials and Methods. Throughout
the manuscript, we will refer to this method as the “one centered” method, because the null distribution is centered around the identity matrix, rather than a matrix of zeros, as in Eq. (3). Correspondingly, we will refer to the version of the STC method obtained by diagonalizing Eq. (3) as the “zero-centered” method.

In essence, both the one-centered and the zero-centered versions are similarly affected by inhomogeneous sampling variability.

The authors of [7] proposed a slightly different definition of the null distribution and a nested hypothesis technique for significance testing. For the model cell simulations we used both significance analysis methods, in both the “zero-centered” and “one-centered” STC formulations, and obtained similar results. For the rest of this paper we will refer to our significance testing method as the “global” one, and focus mainly on the “zero-centered” formulation of the STC method. Using this combination the important effects of the strong stimulus correlations on the analysis are more easily understood.

Model cells presented with strongly correlated noise

We begin with an illustration of the problems that arise when the STC method is used to analyze neural responses to strongly correlated Gaussian noise (Fig. 1). We simulated a model neuron where the neuronal responses were modulated by stimulus projections onto a single dimension (termed here the relevant feature). The stimuli were constructed to match the second-order statistics from the set of images in the van Hateren dataset [38] (see Materials and Methods). In this example obtained for dataset of a moderate size, no eigenvalues fell outside of the 98\% confidence intervals (shaded area indicates 98\% confidence intervals for the support of the null distribution). No eigenvalues of \( \Delta C \) are found to be significant (shaded area indicates 98\% confidence intervals for the support of the null distribution) (C) Rank ordered eigenvalues (black) plotted with the null distribution (blue). (D) Nested rank-wise significance testing. The highest ranked eigenvalues of \( \Delta C \) are within the 98\% confidence intervals derived from the null distribution constructed for each rank separately (see Materials and Methods for details). (E) For each random spike train we computed \( \delta_2^2 \), the variance of the projection of the spike-triggered stimulus on the relevant feature \( \phi \) (distribution shown in yellow). The purple line indicates \( \delta_2^2 \) for the real spike train, suggesting the spike train contains enough signal to determine the relevant feature as significant. Inset shows the relevant feature, a 16 x 16 image patch (\( p = 256 \)). Simulation details: \( N = 1189, N_{spike} = 329, 250 \) repetitions to find \( \Delta C^{null} \).

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Figure 1. Spike triggered covariance analysis of simulated spike trains of a model with a single feature orthogonal to the coherent mode. (A) Inputs are plotted when projected on the eigenvectors corresponding to the largest eigenvalues of \( \Delta C \) (in units of pixel illumination). Marginal distributions are plotted for each dimension. Inputs that elicited a spike are shown in red, and those that did not in blue. By construction, the change in variance is larger along the first dimension. (B) The empirical eigenvalue distribution of \( \Delta C \) (black) compared to the null distribution (blue). (C) Rank ordered eigenvalues (black) plotted with the null distribution (blue). (D) Nested rank-wise significance testing. The highest ranked eigenvalues of \( \Delta C \) are within the 98\% confidence intervals derived from the null distribution constructed for each rank separately (see Materials and Methods for details). (E) For each random spike train we computed \( \delta_2^2 \), the variance of the projection of the spike-triggered stimulus on the relevant feature \( \phi \) (distribution shown in yellow). The purple line indicates \( \delta_2^2 \) for the real spike train, suggesting the spike train contains enough signal to determine the relevant feature as significant. Inset shows the relevant feature, a 16 x 16 image patch (\( p = 256 \)). Simulation details: \( N = 1189, N_{spike} = 329, 250 \) repetitions to find \( \Delta C^{null} \).
eigenvalue (for example, see eigenvalue marked \( \lambda_1 \) in Fig. 2A). The corresponding eigenvector has all positive components [28,30] and is often referred to as the “coherent mode” [34]. To understand why such a coherent mode appears, one can consider the case where the correlations decrease only slightly over the range of image patches used to compute the covariance matrix. In this case, the correlation values in different image patches will be approximately the same. Such a matrix will have one outstanding eigenvalue with a corresponding eigenvector that has equal weights approximately the same. Such a matrix will have one outstanding mode that appears once the mean of matrix elements exceeds their standard deviation. The eigenvector corresponding to the outstanding eigenvalue is \( \frac{1}{\sqrt{p}}(1, \ldots, 1) \). The semicircle law appears because matrices are no longer positive-definite after shuffling. However, the outstanding eigenvalue is located at exactly the same value as the outstanding eigenvalue of the natural scenes covariance matrix \( C_{\text{pop}} \) (see Fig. 2C).

In our analysis of the van Hateren database, the largest eigenvalue tends to be at least 3–4 times larger than the second largest eigenvalue. This shows how strong the coherent mode is compared to other modes. The principal components ranked below the coherent mode form a collection of orthogonal “edge detectors”, some of which correspond to an eigenvalue still much larger than the mean eigenvalue of \( C_{\text{stim}} \), a signature of the stimulus’ heavy-tailed covariance spectrum. Such large disparities in variance along the different dimensions in the stimulus space make it problematic to directly compare changes in variance induced by the observation of spikes along these different dimensions.

The detailed structure of sampling variability in the estimation of eigenvectors and eigenvalues can be understood in terms of the Spiked Wishart ensemble [35,36]. In the Spiked Wishart matrix model, the true (population) covariance eigenvalues are all equal to one, except for a small number \( v \ll p \) of outstanding modes with eigenvalues larger than one \( (1 + \tau_1, 1 + \tau_2, \ldots, 1 + \tau_v, 1, \ldots, 1) \), where \( p \) is the stimulus dimensionality. The distribution of sample covariance eigenvalues \( g_N(\lambda) \) for a finite number of inputs has a positive bias, with the following analytical expressions [36]:

\[
g_{SW}(\lambda) \propto (p-v)g_{MP}(\lambda) + \sum_{i=1}^{v} \rho_i
\]

where

\[
\rho_i \sim N \left( (1 + \tau_i) \left( 1 + \frac{1}{\gamma i} \right), \frac{\sigma_i^2}{N} \right)
\]

\[
\sigma_i^2 = 2(1 + \tau_i)^2 \left( 1 - \frac{1}{\gamma i} \right)
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The distribution of matrix elements \( \chi_{ij} \) is often referred to as the “coherent mode” [34]. To understand why such a coherent mode appears, one can consider the case where the correlations decrease only slightly over the range of image patches used to compute the covariance matrix. In this case, the correlation values in different image patches will be approximately the same. Such a matrix will have one outstanding eigenvalue with a corresponding eigenvector that has equal weights approximately the same. Such a matrix will have one outstanding mode that appears once the mean of matrix elements exceeds their standard deviation. The eigenvector corresponding to the outstanding eigenvalue is \( \frac{1}{\sqrt{p}}(1, \ldots, 1) \). The semicircle law appears because matrices are no longer positive-definite after shuffling. However, the outstanding eigenvalue is located at exactly the same value as the outstanding eigenvalue of the natural scenes covariance matrix \( C_{\text{pop}} \) (see Fig. 2C).

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\]

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\]
numerical simulations we verified that, although the Spiked Wishart ensemble is only an approximation to the covariance matrices derived from natural stimuli, Eqs. (7) and (9) accurately describe the scaling of the variance and the mean of sample eigenvalues as $N$ increases.

In addition to biases in eigenvalue estimates, there are also biases in the estimation of eigenvectors. The dot product between the true (population) $i$th eigenvector $f^0_i$ and the $i$th eigenvector $f^{(1)}$ of the sample covariance approaches

$$|f^{(1)}_i, f^0_i| \to \sqrt{\frac{1 - 1/(\gamma_i \tau_i)}{1 + 1/(\gamma_i \tau_i)}}$$

(11)

In other words, the “mixing” of the outstanding sample eigenvectors seen in Eq. (11) (note the dependence of this mixing on $N$ through $\gamma$) as well as the variance and bias in the sample eigenvalues seen in Eq. (7) means that whitening cannot be exact.

In the context of the spike triggered covariance the consequences of such properties of the distribution of sample eigenvalues are twofold. First, Eq. (9) indicates that the variance of the outstanding eigenvalues around their mean increases with the square of their value and is inversely proportional to the number of samples. Thus, for sample sizes that are not much larger than the stimulus dimensionality ($1 < \gamma_{\text{spike}} < 10$) in the simulation results presented in Fig. 3A), the increased variance of the outstanding sample eigenvalue means that $C_{\text{null}}$ and $C_{\text{sim}}$ will not cancel each other exactly along that vector. Second, the mean estimate contains a positive bias relative to the population values, cf. Eq. (7). The combination of these two effects widens the null-distribution used to test the significance of the resulting eigenvectors, effectively masking features that should otherwise be identified as being relevant.

**Pre-whitening**

One way to compensate for the symmetry breaking effects caused by strong correlations in the input space is to equalize variances before applying the STC method. This is the essence of the “one-centered” formulation of the STC method [7]. In principle, this “whitening” should work with Gaussian stimuli with any covariance structure. However, as discussed above, in the case of strongly correlated stimuli, the estimation of eigenvalues (i.e variances along different dimensions in the input space) possesses strong variability, cf. Eq. (7). As a consequence, normalization by a variance estimated from one part of the dataset does not fully remove correlations in a different subset of the data. With increasing dataset size, the estimate of the variance along the coherent mode improves. However, because the absolute value of variance is not relevant in the pre-whitening method, dimensions with smaller variance can cause just as much contamination as the coherent mode. In addition, the estimation of variance along dimensions corresponding to $\tau_i$ just larger than $1/\sqrt{\gamma}$ remains poor for large $N$. If $\tau_i = 1/\sqrt{\gamma} + \epsilon$ the sample eigenvalue estimation error diverges as $\sqrt{\gamma}$, as follows from Eq. (8). In other words, as the number of samples $N$ and $\gamma$ increase, the bulk of the distribution narrows, and new eigenvalues separate from the bulk. It is these eigenvalues with intermediate values that are poorly determined and make it problematic to equalize variance along different dimensions. Another signature of this phenomenon is that $f^{(1)} f^{(1)} \approx 0$ for these dimensions, as follows from Eq. (11). Thus, these dimensions are poorly estimated from the sample covariance and, as a consequence, the variance along one stimulus dimension in the training set will be inappropriately used to normalize variance along a different stimulus dimension in the test set. Altogether, we observed that pre-whitening stimuli did not improve the estimation of relevant stimulus features compared to the zero-centered method, compare panels A and B in Fig. 3.

Intuitively, in the zero-centered method the dimensions with the largest variance provide the largest uncertainty in variance estimation, whereas in the one-centered version the problematic dimensions change depending on the dataset size, and are not easily identified a priori.

We have also explored the possibility of using a pseudoinverse of the covariance matrix instead of the full inverse to normalize variance along different dimensions (see Materials and Methods for details). When using the pseudoinverse (instead of the inverse), stimulus dimensions with small variance in the stimulus ensemble are removed to avoid noise amplification along these dimensions (see Materials and Methods for details). However, an immediate consequence of choosing a small pseudoinverse order $k$ ($\approx p/10$) is that the stimulus dimensionality is reduced to $k$. This implies that the effective $\gamma$ of the problem is now $\gamma_k = N/k$, i.e. $p/k$ times larger than $\gamma$. This could work well in some cases as illustrated in Fig. 3I. Here, in simulations based on a small number of spikes, the use of pseudoinverse can help recover one or two significant features while the standard zero-centered method fails to find any. However, the use of pseudoinverse only helps within a very narrow band of small pseudoinverse orders. This band may be difficult to determine when analyzing real neural data. In addition, this procedure limits the reconstruction to a linear combination of only a few leading stimulus dimensions. In many cases, the relevant features do include components along stimulus dimensions with smaller variance, and in those cases, the effective increase in $\gamma$ will not improve the performance of the STC method. Indeed, one observes that in cases where two significant dimensions are obtained by using substantial reduction in dimensionality of the pseudoinverse, the resulting dimensions have the subspace projection onto the model features of $\sim 0.6$ whereas this value is $\approx 0.8$ when using the full inverse and a larger number of spikes to obtain for a comparable effective $\gamma$ (Fig. 3I).

Finally, in the regime where $k \approx p$ (i.e. “almost full” inverse), the prewhitening approach works just as well as the “zero-centered” formulation, and a relatively high value of the signal-to-noise ratio parameter $\gamma_{\text{spike}}$ is required for recovery of the full relevant subspace.

**Correction scheme**

As another way to compensate for the symmetry breaking effects caused by strong correlations in the input space, we propose to modify the “zero-centered” formulation of the STC method in the following way. Because the largest drop in variance is between the coherent mode and other dimensions, we propose here to test the significance of changes in variance separately along the coherent mode and in the subspace orthogonal to it. Explicitly, to do the analysis in the $p-1$ dimensional subspace, the coherent mode $f^{(1)}$ is projected out of all stimuli. If $s$ is a stimulus vector and $f^{(1)}$ normalized to length 1, one can perform the STC analysis using $s$ instead of $s$ where:

$$s_i = s_i - \frac{1}{p} \sum_{j=1}^{p} f^{(1)}_j s_j.$$  

(12)

In this approach the correct number of relevant dimensions is determined by evaluating significance in the subspace orthogonal
Figure 3. Spike triggered covariance analysis of a model neuron with two relevant features orthogonal to the coherent mode. Spectra of $\Delta C$ for increasing dataset size in the case of strongly correlated Gaussian noise (A–C) and white noise (D). (A–D) The range of spikes covered is from $N_{\text{spike}} \approx p$ to $N_{\text{spike}} \approx 22p$. Panel B shows the results using the pre-whitening ("one-centered") method, and panel C shows the results after evaluating significance in the subspace orthogonal to the coherent mode. Each vertical line shows the result of a single simulation. Significant (insignificant) eigenvalues are shown in red (black), and the range of the null distribution (1000 evaluations of $\Delta C_{\text{null}}$, 98% confidence interval) is shown in gray. (E–H, left) Gray shaded area is the support of the null distribution, which itself is plotted in blue. The significant (insignificant) portion of the spectrum of $\Delta C$ is plotted in red (black). These example spectra, with the corresponding significant vectors, are for conditions with a small number of spikes (indicated by an orange star in A–D) for which both of the formulations find no significant dimensions. $N \sim 1189$, $N_{\text{spike}} \sim 300$ for the correlated stimulus condition in panels E–G, $N \sim 1189$, $N_{\text{spike}} \sim 280$ for the white stimulus condition in panel H. (E–H, right) Results of the nested significance testing. We note that the second ranked eigenvalue in panel E is outside of its confidence interval, but still cannot be found to be significant. This happens because of the noise along the coherent mode. (I) STC analysis using all pseudoinverse orders using the nested significance testing with 99% confidence intervals (large box) compared to the analysis using our proposed correction scheme. Black means no significant features were found for that combination of $N_{\text{spike}}$ and pseudoinverse order. Cold (hot) colors indicate that one (two) features were found to be significant. The corresponding color bars on the right indicate the geometric average of the feature projections on the two model dimensions (cold colors) or the subspace overlap with the model, cf. Eq. (36) (hot colors). (J) Results when STC is performed using the proposed correction scheme. The two relevant dimensions (black frame) and the decorrelated significant features (red frame) have subspace overlap of 0.82. The models were defined such that the mean firing rate remained unchanged between the two stimulus conditions.

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to the coherent mode and then adding back their projections on the coherent mode from the corresponding eigenvectors evaluated in the full input space (see below).

We find that considering the coherent mode separately from the rest of stimulus dimensions reduces the value of $\gamma_{\text{spike}}$ for which the full relevant subspace is found to be significant by a factor of 10 (Fig. 3C). This improvement can be approximated from Eqs. (7) and (8). Assuming the cell’s relevant subspace is exactly orthogonal (Fig. 3C), this corresponds to a predicted fold improvement. Following the correction, the number of significant dimensions per cell increased from $1.1 \pm 0.2$ to $4.6 \pm 0.5$ (see Fig. 5A for the full population values). The dimensionality of the relevant subspace increased for 21 out of 22 cells. For one cell, we were unable to find a significant dimension either before or after the correction of the method. The distributions of null eigenvalues used to determine which of the eigenvectors of $\Delta C$ are significant (Fig. 5B,C) became much more narrow when evaluated in the subspace orthogonal to the coherent mode.

**Application to retinal ganglion cells**

We now demonstrate the importance of this correction scheme by analyzing recordings of 22 salamander retinal ganglion cells (RGCs). These neurons were probed with a correlated noise stimulus whose covariance matrix was matched to that of natural visual stimuli. Without correcting for the presence of the coherent mode, the STC analysis yielded no significant dimensions for a third of the cells, and very few for the rest (Fig. 5). This happens because the eigenvalue corresponding to the coherent mode injects large eigenvalues into the null eigenvalue distribution (as seen in Eq. (8)), thus masking the cell’s true relevant features. Following the correction, the number of significant dimensions per cell increased from $1.1 \pm 0.2$ to $4.6 \pm 0.5$ (see Fig. 5A for the full population values). The dimensionality of the relevant subspace increased for 21 out of 22 cells. For one cell, we were unable to find a significant dimension either before or after the correction of the method. The distributions of null eigenvalues used to determine which of the eigenvectors of $\Delta C$ are significant (Fig. 5B,C) became much more narrow when evaluated in the subspace orthogonal to the coherent mode.
in most cases can only be done for simple eigenvalue distributions [43].

The treatment of the artifacts caused by a large coherent mode present in the data has been previously discussed in analyses of stock-markets [44,45], evolution of proteins [46], and Human Immunodeficiency Virus (HIV) mutations [34]. In these cases, the extra dimension was removed and the resulting covariance structure was compared against the Marcˇenko-Pastur eigenvalue distribution that assumes no correlation between the variables and uniform variable variances. The case of reverse correlation

Figure 4. Spike triggered covariance analysis of a model neuron with one relevant feature that has a large component along the coherent mode. Spectra of $\Delta C$ for increasing dataset size in the case of strongly correlated Gaussian noise (A,B) and white noise (C). (A–C) The range of spikes covered is from $N_{\text{spike}} \approx 1.3p$ to $N_{\text{spike}} \approx 34p$. Panel B shows the results after evaluating significance in the subspace orthogonal to the coherent mode. Each vertical line shows the result of a single simulation. Significant (insignificant) eigenvalues are shown in red (black), and the $[1,99]$ percentile range of the null distribution ($1000$ evaluations of $\Delta C_{\text{null}}$) is shown in gray. (D–F) Gray shaded area is the support of the null distribution, which itself is plotted in blue. The correct feature is found using both stimulus conditions and both the original formulation of the STC method and our proposed correction. $N = 1995$, $N_{\text{spike}} = 655$ for the correlated stimulus condition in panels D and E, $N = 1995$, $N_{\text{spike}} = 630$ for the white stimulus condition in panel F (indicated by an orange star in panels A–C). Insets to panels D–F show the recovered feature (decorrelated in panels D,E) and the nested significance testing which does not affect the results. Black framed inset to panel D shows the model feature. The models were defined such that the mean firing rate remained unchanged between the two stimulus conditions.

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Testing for significance

We describe two approaches for determining significance of candidate features that were previously described in the literature: global and nested. When applied to our datasets, both of the approaches yielded similar results.

Global null distribution. Eigenvalues of $ΔC$ are identified as significant if they lie outside the $[z, 100 − z]$ percentile interval of the null distribution, where parameter $z$ specifies the level of significance. The null distribution is constructed by computing many realizations of the matrix $ΔC^{null} = C^{null} − C^{stim}$.

If $z = 0$ is used, the number of randomized spike trains is inversely proportional to the confidence interval with which significance is determined.

To describe how matrix $C^{null}$ is computed, we recall that

$$C^{spike} = \frac{1}{N_{spike} - 1} \sum_{k=1}^{N_{spike}} (\langle x_j^k - \langle x_j \rangle \rangle (\langle y_j^k - \langle y_j \rangle \rangle), \quad (15)$$

where $\langle x_j \rangle$ and $\langle y_j \rangle$ are the spike-triggered average of the $i$th stimulus component and spike times are denoted as $\{t_k\}_{k=1}^{N_{spike}}$.

The matrix $C^{null}$ is computed in the exact same manner, but instead of the spike train $\{t_k\}_{k=1}^{N_{spike}}$, we use random spike trains $\{\tilde{t}_k\}_{k=1}^{N_{null}}$.

$$C^{null} = \frac{1}{N_{null} - 1} \sum_{k=1}^{N_{null}} (\langle x_j^k - \langle x_j \rangle \rangle (\langle y_j^k - \langle y_j \rangle \rangle). \quad (16)$$

Note that there are just as many random spike times $\tilde{t}$ as real spike times $t$. Moreover, when the spike train has a meaningful temporal structure, the random spike train can be obtained by a random shift of $\{\tilde{t}_k\}_{k=1}^{N_{spike}}$, defined for all $k = 1 \ldots N_{spike}$ and for a random integer $m$ chosen uniformly between 1 and $N$ [20]:

$$\tilde{t}_k = (t_k + m) \mod N. \quad (17)$$
Using all the realizations of Cnull computed (i.e. all the randomly chosen m’s), the eigenvalues of ΔCnull compose the null distribution.

**Nested significance testing.** Significance can also be tested in a nested fashion using p rank-ordered null distributions. This method is detailed in [7]. For completeness we briefly describe it here. For each of the randomized spike trains the eigenvalues of ΔCnull (or Cnull for the pre-whitened formulation, see Eq. (25) below) are rank ordered. The eigenvalues of each order from all the randomized spike train compose a separate null distribution. Then, for each of these p distributions we found a confidence interval. If the smallest eigenvalue of ΔC (or C^A) is smaller than the lower bound of its relevant confidence interval (or if the largest eigenvalue is larger than the upper bound) the corresponding eigenvectors are determined to be significant. These eigenvectors are then projected out of the stimulus and the analysis is repeated until no eigenvalues are found to be significant. Note that according to this method some eigenvalues of ΔC (or C^A) can be identified as insignificant but still be outside of the confidence interval computed for their rank if the largest eigenvalue lies within its confidence intervals (see Fig. 3E, right).

**Decorrelation within the STC method**

Within the STC method, stimulus correlations need to be removed from the estimates of eigenvectors obtained by diagonalizing matrix ΔC. This correction is needed, because the eigenvectors of ΔC have a form \( \sum_{n=1}^{p} C_{i,j} \phi_j \), where \( \phi_j \) describe components of one of the relevant features [20]. As described above, one may wish to use a pseudoinverse, instead of the full inverse of the matrix C to minimize noise amplification at higher spatial frequencies. Assuming that the eigenvalues are ordered to be monotonically decreasing, the pseudoinverse of order \( k \) is given by

\[
C^{-1}_p(k) = \sum_{n=1}^{k} \frac{1}{\lambda_n} f_i^{(n)} f_j^{(n)}. \tag{18}
\]

In the analysis of data from retinal ganglion cells, the optimal order of the pseudoinverse was determined in the following way. The dataset was divided into the training and test sets. The features were computed by diagonalizing the matrix ΔC, cf. Eq. (3), in either the full input space or in the space orthogonal to the coherent mode using the training set. Following that, the optimal pseudoinverse order \( k^* \) was selected as the one that yielded decorrelated features that convey the most information about, or give the largest predictive power for, the neural response. Explicitly,

\[
k^* = \arg\max_{k \in [1, \ldots, p]} I(k), \tag{19}
\]

\[
I(k) = \int d\vec{x} P_n(\vec{x}|\text{spike}) \log \frac{P_n(\vec{x}|\text{spike})}{P_k(\vec{x})}, \tag{20}
\]

where \( P_n(\vec{x}) \) is the probability distribution of the projections of stimuli onto the \( d \) significant eigenvectors (\( q_i \)), decorrelated by \( C^{-1}(k^*) \). \( \bar{q}_i = C^{-1}(k^*) q_i \) are the decorrelated significant features, and:

\[
\bar{\vec{x}} = (x_1, \ldots, x_d), \tag{21}
\]

\[
x_i = q_i \cdot \bar{s}. \tag{22}
\]

**Pre-whitening**

As an alternative to removing stimulus correlations from the eigenvectors of ΔC, one can remove stimulus correlations from each of the stimulus vectors, prior to the diagonalization of ΔC, a procedure that is known as pre-whitening [7].

The sample stimulus covariance matrix from Eq. (2) can be written in terms of eigenvalues \( \hat{\lambda}_n \) and eigenvectors \( f_i^{(n)} \) as

\[
C^{\text{stim}} = \sum_{n=1}^{p} \hat{\lambda}_n f_i^{(n)} f_j^{(n)}. \tag{23}
\]

We can now define a matrix \( C^{\text{w}} = \sum_{n=1}^{p} \hat{\lambda}_n^{-1/2} f_i^{(n)} f_j^{(n)} \). Then, the analogue of ΔC in the “one-centered” formulation is given by:

\[
C^A = C^w C^{\text{spike}} C^w. \tag{24}
\]

This procedure is equivalent to whitening each of the stimulus frames independently (by multiplying it with \( C^w \)) and then computing the spike-triggered covariance.

In the limit of infinite data, the null hypothesis corresponds to \( C^{\text{spike}} = C^{\text{stim}} \). In this case \( C^A = I \). For a dataset of finite size, the null distribution is computed from many realizations of the matrix

\[
C^{A\text{null}} = C_n C^{\text{null}} C_n, \tag{25}
\]

where \( C^{\text{null}} \) is defined by Eq. (16). The eigenvalues of \( C^A \) (most of which are close to 1) can then be compared to the null eigenvalue distribution, using either the nested or global comparison tests described above.

In Fig. 3 we analyzed the simulated spike trains using every pseudoinverse order of \( C^{\text{stim}} \). The prewhitening is then done using this matrix \( C^{-1}(k^*) \), Eq. (18) instead of the full rank matrix \( C^{-1}(p) \).

Performing the pre-whitened STC analysis using all pseudoinverse orders is equivalent to testing \( p \) models. Therefore, the confidence interval of the null distribution should be adjusted from the \([z,100-z]\) percentile range to \([z_{DS},100-z_{DS}]\), where \( z_{DS} \) is the Dunn-Sidak correction:

\[
z_{DS} = 100 \left[ 1 - \left(1 - \frac{z}{100}\right)^p \right] \approx \frac{z}{p} \tag{26}
\]

**Relevant features in the full stimulus space**

We recall that according to Ref. [20], the significant eigenvectors of ΔC can be written as

\[
e_i = \sum_{n=1}^{p} \hat{\lambda}_n f_i^{(n)} f_j^{(n)} \phi_j. \tag{27}
\]

Thus, the eigenvectors of ΔC represent a sum of projection operators onto the principal components of the stimulus ensemble.
When we perform the STC method in the subspace orthogonal to the first principal component of the stimulus, the eigenvectors of $\Delta C$ can be written as

$$\tilde{e}_i = \sum_{n=1}^{p} \tilde{e}_n f_i(a_n f_j)$$

(28)

(the coherent mode is exactly the vector $f^{(1)}$).

Comparing expressions for the eigenvectors of $\Delta C$ and $\Delta C$, one observes that there is a one-to-one correspondence between them. This correspondence can be identified based on proportionality in components along second, third, and other principal components:

$$\tilde{e}_i f^{(2)} = \tilde{e}_j f^{(3)} = \ldots = \tilde{e}_i f^{(r)}$$

(29)

for any $i > 1$. In sum, once the eigenvector $\tilde{e}$ is found to be significant in the subspace orthogonal to $f_j$, the eigenvector that should be identified as significant in the full stimulus space is $e$ that satisfies the condition of Eq. (29).

Model neurons

The nonlinearity was chosen to be a logistic function because such functions maximize the cell’s noise entropy and thus minimize the assumptions imposed on the cell’s response [48]. Using the models, we generated simulated spike trains in response to either a white or a correlated noise stimulus.

The model used in Fig. 3 (model “A”) had a two dimensional relevant subspace with features orthogonal to the coherent mode. The probability of spiking was modeled to increase when the projection of the stimulus on either of the preferred features was large in absolute value (representing a logical OR function). If

$$\phi_1, \phi_2$$

are the preferred model features and $s'$ is the stimulus presented at time $t$ (here, the $\phi$'s and $s'$ are $p = 256$ dimensional vectors) then the probability of a spike at time $t$ is:

$$p^{A}_t(s' | s) = 1 - \prod_{i=1,2} \left[ 1 - \frac{1}{1 + e^{(s, \phi_i - s')/\delta_{A}^{i}}} \right]$$

(30)

where $\delta_A^i$ are parameters that determine the width and (soft) thresholds of the sigmoid nonlinearities for the model.

We have also considered the case where the projection of the stimulus on the features was not taken in absolute value, corresponding to a monotonic nonlinearity. In that case (model “A1”, used in Fig. 1) the model was one dimensional, so the probability of a spike is

$$p^{A1}_t(s' | s) = \frac{1}{1 + e^{(s, \phi_1 - s')/\delta_{A1}}},$$

(31)

The effects described above were observed for both symmetric (Fig. 3) and monotonic (Fig. 1) nonlinearities.

The second model had one relevant input feature $\phi^B$ with a large component along the coherent mode. In this case, the probability of a spike was modeled as:

$$p^{B}_t(s' | s) = \frac{1}{1 + e^{(s, \phi^B - s')/\delta_{B}}}$$

(32)

where $\delta_B$ and $\delta_B$ are the width and the threshold of the sigmoid nonlinearity of this model.

In units of the standard deviation of the projection of the stimulus on the model features $\{\sigma_{white}, \sigma_{corr}\}$ the model parameters were chosen to be:

$$\frac{\delta_{A1}^1}{\sigma_{white}} = 2.3, \frac{\delta_{A1}^2}{\sigma_{corr}} = \frac{\delta_{A1}^A}{\sigma_{white}} = 0.73$$

(33)

$$\frac{\delta_{A1}^1}{\sigma_{white}} = 1.02, \frac{\delta_{A1}^1}{\sigma_{corr}} = 0.85$$

(34)

$$\frac{\delta_{A1}^B}{\sigma_{white}} = 0.89, \frac{\delta_{A1}^B}{\sigma_{corr}} = \frac{\delta_{A1}^B}{\sigma_{white}} = 0.28$$

(35)

Subspace overlap

The overlap measure we use when the dimensionality of the relevant subspace is greater than one is given by [49]:

$$\mathcal{O}(\Phi, \Psi) = \frac{|\det \Phi^T \Psi|}{\sqrt{|\det \Phi^T \Phi| |\det \Psi^T \Psi|}}$$

(36)

where $\Phi$ and $\Psi$ are $p \times d$ matrices that hold the model and computed features, respectively, $p$ is the input dimensionality, and $d$ is the number of relevant features in the model.

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Author Contributions

Conceived and designed the experiments: JA RS MJB TOS. Performed the experiments: JA RS. Analyzed the data: JA RS. Wrote the paper: JA RS MJB TOS.

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