## Examples of use of NIT for studying the role of correlations in neural populations

We exemplify, using simulated data, how to use NIT to study how correlations between the activity of different neurons shape the information encoded in populations of neurons ranging from pairs to tens of neurons.

Understanding how noise correlations, defined as the correlations of the activity of different neurons across trials with the same sensory stimulus, shape the encoding of sensory information has been a major question in systems neuroscience, because it reveals the emergent properties of population codes.

We simulated three scenarios (sketched in Figure 1A), which captured three main ways in which correlations have been reported to influence population coding. In each case, we created correlated spike trains of a population of N = 20 neurons in the tonic low-rate low-information regime described above (mean responses to the two stimuli were low and spikes had a time-independent probability of being emitted). In the first scenario (no noise correlations, left column of Figure 1), the spike trains were independently generated for each neuron with Poisson statistics and with lower rate to the first stimulus and a higher rate to the second stimulus. This scenario had zero noise correlations but had positive signal correlations (the correlations across the trail averaged responses to different stimuli) because each of the neurons had lower trial-averaged responses to stimulus 1 and higher trial-averaged responses to stimulus 2). In the second and third scenarios we created correlations between the neurons by generating responses each stimulus that were the sum of an independent Poisson process (with an outcome generated independently for each neuron) and a shared Poisson process (whose outcome was the same across neurons). The second scenario (information-limiting noise correlations, central column of Figure 9) had the same trial-averaged rates as the first scenario (and thus positive signal correlations) but also positive noise correlations that were only weakly stimulus dependent (the pairwise Pearson noise correlation was 0.2 for stimulus 1 and 0.1 for stimulus 2). The third scenario had the same trial-averaged rates for the two stimuli (2 Hz) but had a strong stimulus-modulation of the strength of correlations (the pairwise Pearson noise correlation was 0.5 for stimulus 1 and 0 for stimulus 2).

We then used NIT to evaluate the effect of noise correlations strength on the stimulus information carried by populations of neurons. We first used the information breakdown (Pola et al., 2003) on pairs of neurons to break down (using the direct plugin method, with no decoding step) the total information carried by each pair of neurons into the contribution of different correlational components (Figure 9B). In first scenario, the information breakdown correctly retrieved that noise correlations, being null, did not contribute to information, and that the only redundancy between cells was due to the similarity of trial-averaged response profiles (negative component). In the second scenario, the information breakdown confirmed the prediction that noise correlations overall decreased the amount of information because signal and noise correlations were both positive (negative term, which captures this phenomenon, was larger than the very small amount of information added by their weak stimulus dependence, term). In the third scenario, the information breakdown correctly found that no information was carried by the firing rate of single cells (null and terms) and that all the information was carried by the stimulus dependence of noise correlations (positive and large term).

While the information breakdown can correctly capture the pairwise coding mechanisms present in the population with precision and detail, in practice it is difficult to extend its use beyond pairs and triplets because of the exponentially large number of trials needed to directly sample the probabilities of responses of neural populations. It is known from theoretical considerations that the impact of noise correlations is expected to proportionally increase with population size with respect to the contribution of firing rates of individual cells (because the latter scales linearly and the former quadratically with population size). Thus, the overall impact of correlations on large populations can only be computed by estimating information from the full population rather than from pairs. To evaluate the role of correlations in information coding, we therefore used the NIT implementation of computation of mutual information from the confusion matrix of a cross-validated SVM decoder of the stimulus from population activity. With this approach, the role of correlations cannot be computed analytically (as in the information breakdown) but it can be evaluated numerically (all with options included in NIT) comparing the information carried in real simultaneously recorded population spike trains (which contain correlations) to the “shuffled” information contained in pseudo-population responses obtained by randomly shuffling responses across trials with the same stimulus. The shuffled pseudo-population responses have the same single cell properties as the real data, but no noise correlations. Because the term sets an upper bound to the information that is lost when using decoders that ignore correlations (Latham and Nirenberg, 2005), the presence of stimulus-dependent correlations that enhance information coding can be investigated comparing the information extracted, from real unshuffled population responses, using linear decoders such as linear SVMs (that are only sensitive to information carried by differences across stimuli of individual cells) with non-linear decoders such as radial basis function (RBF) SVMs (that can also capture information carried by stimulus dependence of correlations).

We first applied the shuffling and decoding population analysis to spike rates (Figure 9C). When applied to the first scenario, the shuffling and decoding formalism correctly found that correlations did not carry any information (because information values were the same for real and shuffled data, and for linear and RBF SVMs). When applied to the second scenario, the shuffling and decoding formalism revealed that the information-limiting effect of correlation at the population level was large (it nearly halved the total information, compared to a relatively small effect at the pairwise level), confirming both theoretical scaling expectations and recent reports of large effects of correlations when considering larger populations. Also, the results suggest the presence of a more sizeable positive contribution of stimulus-dependent correlations (because the information decoded with radial SVM is larger than the information decoded with a linear SVM). When applied to the third scenario, the shuffling and decoding population analysis correctly found that firing rates of individual cells did not contribute any information (information from shuffle data was null with any decoder, and information in real population responses was zero with linear decoders), and that instead considerable information was available from the stimulus dependence of noise correlations (as revealed by the large information found only with radial SVM decoding in real population responses). To verify that correct results could also be found with calcium imaging responses rather than spike rates, we created from the spike trains also simulated calcium traces and we found comparable results and from the simulated calcium (Figure 1D).

The complementarity of using both the information breakdown and information theory with SVM decoders on the same dataset and the same algorithms implemented in NIT was demonstrated in (Curreli et al., 2022) with populations of neurons and/or astrocytes recorded with 2P calcium imaging. The power of these decoding algorithms for analyzing larger populations of hundreds of cells recorded with calcium imaging was demonstrated in (Valente et al., 2021).

In sum, our simulations together with previous studies illustrate the power of using NIT to precisely determine the role of correlations among populations of even tens to hundreds of cells in datasets recorded during cognitive tasks.



**Figure 1. Effect of noise correlations on the encoding of stimulus information in neural populations**. (**A**) Depiction of how correlations shape the response distributions, and therefore the stimulus information encoded by pairs of neurons, in three simulated scenarios: no noise correlations (scenario one, left), information limiting signal correlations (scenario two, middle) and pure stimulus-dependent noise correlations (scenario three, right). Responses to stimulus 1 and stimulus 2 are depicted as purple and green ellipses, respectively. (**B**) Pairwise information breakdown of spike rates in scenario one (left), scenario two (middle), and scenario three (right). Three stars above bars indicate that the correspondent information term was significantly different from zero with p < 0.001, stars omission indicates that terms were not significantly different from zero, p 0.05 (two-tailed t test for terms that could be both positive or negative, and one-tailed t test for terms that could either be larger or lower than zero). Error bars are standard deviations across repetitions of the simulation (N=50). (**C**) Population decoded information from spike rates in scenario one (left), scenario two (middle), and scenario three (right). Linear and RBF SVMs information values are reported in blue and red, respectively. Information measured from the original (unshuffled) data is depicted with a dark hue, while information measured from shuffled data has a light hue. Error bars are standard deviations across repetitions of the simulation (N=50). **D**) Same as panel C but for simulated calcium traces, using the estimated calcium metric for information decoding.