



The implications of categorical and category-free mixed selectivity on representational geometries

Matthew T. Kaufman^{1,a}, Marcus K. Benna^{2,a}, Mattia Rigotti^{3,a},
 Fabio Stefanini^{4,a}, Stefano Fusi⁴ and Anne K. Churchland⁵

Abstract

The firing rates of individual neurons displaying mixed selectivity are modulated by multiple task variables. When mixed selectivity is nonlinear, it confers an advantage by generating a high-dimensional neural representation that can be flexibly decoded by linear classifiers. Although the advantages of this coding scheme are well accepted, the means of designing an experiment and analyzing the data to test for and characterize mixed selectivity remain unclear. With the growing number of large datasets collected during complex tasks, the mixed selectivity is increasingly observed and is challenging to interpret correctly. We review recent approaches for analyzing and interpreting neural datasets and clarify the theoretical implications of mixed selectivity in the variety of forms that have been reported in the literature. We also aim to provide a practical guide for determining whether a neural population has linear or nonlinear mixed selectivity and whether this mixing leads to a categorical or category-free representation.

Addresses

¹ Department of Organismal Biology and Anatomy, Neuroscience Institute, University of Chicago, Chicago, IL, USA

² Department of Neurobiology, School of Biological Sciences, University of California, San Diego, CA, USA

³ IBM Research, Zurich, Switzerland

⁴ Mortimer B. Zuckerman Mind Brain Behavior Institute, Department of Neuroscience, Columbia University, New York, NY, USA

⁵ David Geffen School of Medicine, University of California, Los Angeles, CA, USA

Corresponding authors: Churchland, Anne K. (ACHurchland@mednet.ucla.edu); Fusi, Stefano (sf2237@columbia.edu)

^a Authors contributed equally.

Introduction

A major goal of systems neuroscience is to understand how the activity of neurons relates to behavior. In studying this relationship, the term “mixed selectivity,” an extension of the traditional concept of “neuronal selectivity,” refers to the circumstance in which activity in an individual neuron is modulated by more than one parameter as defined by the experimenter. Although mixed selectivity was first defined for neurons in frontal cortex on a cognitive task [1–4], recent reports have identified neurons with mixed selectivity in multiple other areas for diverse sensory, cognitive, and spatial parameters (see *e.g.*, Refs. [5–12]).

Mixed selectivity is emerging as the norm in many brain areas. The mixing of parameters in the responses of individual neurons has been proposed as a computationally important operation since the early days of neural network theory (see, *e.g.*, the associative units of the perceptron [13]). Though it has been observed frequently, it has been taken as indicative of particular computations instead of being recognized as a general property of cortical coding. For example, mixed selectivity has been described as “tolerance” for nuisance variables in visual areas [14,15], “gain fields” in parietal cortex [16], or uninterpretable encoding in motor cortex [17]. However, understanding the costs and benefits of such representations awaited the study of neural response geometry [2].

Identifying mixed selectivity in neural data

To clarify the definition and characterization of mixed selectivity, an example experimental approach can be helpful. Suppose, for instance, that on each of many successive trials, an animal must choose to go left or right (by moving to a choice port, for instance; Figure 1a, top). The correct choice is specified by the pitch of a noisy tone (Figure 1a, middle). Additionally, the value of a correct left vs. right choice is varied over time, so that each choice can be thought of as occurring in a particular “context”: one in which correct right choices are more rewarding, and another in which correct left choices are more rewarding (Figure 1a, bottom). We define a “condition” combinatorially, as a particular conjunction of

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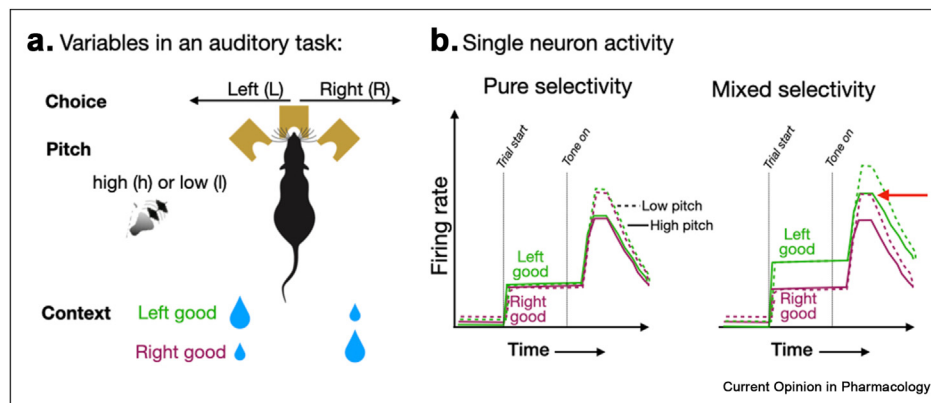
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Figure 1



Example experiment and schematic single-neuron activity. (a) A subject reports a decision by moving to a left or right reward port. This choice is informed by the pitch of a tone. The context of these tones is manipulated (perhaps in blocks) so that sometimes left choices are rewarded more richly ("left good", green), and other times right choices are rewarded more richly ("right good", magenta). (b) Schematic single-neuron responses in the task. Color indicates context; line style indicates pitch. *Left*: neuron with pure selectivity for pitch. *Right*: neuron with mixed selectivity for context and pitch. This leads to equivocal responses (red arrow) if only a single-neuron response is considered.

pitch, noise level (or, more generally, stimulus strength), and context.

When comparing neural activity across conditions, we might observe single-neuron activity that is modulated by only a single variable (pure selectivity, Figure 1b, left) or by more than one task variable—that is, we might observe mixed selectivity in the traditional sense (Figure 1b, right).

Once mixed selectivity is confirmed, we can ask how information is represented across neurons, and how this information might be read out by downstream structures. For these purposes, single-neuron responses are of limited utility, and it becomes necessary to consider the population of neurons collectively. Once we are given the full matrix containing the activity of a population of neurons in response to each experimental condition (Figure 2), we can determine what sort of structure exists in this activity matrix and can consider the computational implications of this structure.

Insights from population activity: linear vs. nonlinear mixing

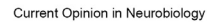
The first way to identify structure in the population response is to analyze the columns of the activity matrix. Each of these columns is an N -dimensional vector (a point in neural activity space, N = number of neurons), which represents the population response to one experimental condition (blue in Figure 2). The arrangement of these points determines the geometry of the neural representation. If the neural responses are well approximated by a linear combination of the task-

relevant parameters (linear mixed selectivity), then the set of points that correspond to all the different conditions typically defines a relatively low-dimensional object (the blue square in the figure). For example, if $N = 3$, as in the plot in Figure 2, and the firing rates of the three neurons depend linearly on two variables, then the points will all lie on a plane. If the variables are binary, they could define a rectangle, as in the figure. More generally, if the N firing rates depend linearly on V variables (with $V \leq N$), the dimensionality of the object defined by all the points that correspond to different conditions will be V .

Neural representations based on linear mixed selectivity neurons are typically low-dimensional, and they share similar generalization properties with what are called disentangled representations in the machine learning community [18]. In these representations, different variables are represented in distinct subspaces, and they allow for better generalization because the coding direction for each variable is independent of coding for the others. For the experiment shown in Figure 1, if all neurons have linear mixed selectivity, then the coding direction for pitch would be the same for the two contexts. This means that a linear decoder trained to report pitch in the first context would readily generalize in the second context, with no need for retraining (cross-condition generalization [8]). These linearly mixed representations have been observed in multiple areas in the brain [8,19–21,12,6].

By contrast, if the neural responses are poorly approximated by a linear combination of the task-relevant

Figure 2



The geometry of the representation, and whether it is categorical or non-categorical, is determined by the matrix of data responses. The matrix (*black*) consists of trial-averaged data and is separated by condition ($r_k(C_j)$ is the firing rate response of neuron k to condition C_j). A single row describes one neuron's response to all the conditions. *Blue*: The columns of this matrix are informative about the representational geometry in the neural activity space. *Red*: The rows of this matrix are informative about whether categories of responses exist in the data. Categorical representations are characterized by clear, distinct clusters in the conditions space. In practice, the existence of categories can be evaluated by visualizing (or analyzing) coefficients from, for instance, a regression that relates the response of each neuron to parameters in the task (pitch and context in our example). The coefficients are indicated by r_k s in the figure. In this example, we are considering only a simple linear regression that ignores higher-order or interaction terms. For this reason, there is no difference between coefficients for low and high-dimensional representations.

parameters (nonlinear mixed selectivity), then the set of points that correspond to all the different conditions typically defines a higher-dimensional object (the blue tetrahedron in the figure). Nonlinear mixed selectivity confers an advantage because this high-dimensional representation allows more flexibility in terms of what can be decoded by a simple linear classifier. This property makes it possible for linear classifiers to pick off any combination of properties desired (just as in some machine learning methods, such as Support Vector Machines [22]). This reduces the computational burden on downstream areas and enables more flexible

representations: for example, using the same sensory stimulus for two different tasks [3]. Nonlinear mixed selectivity has, therefore, been observed where flexibility is most critical, in the monkey frontal cortex [23–25, 3, 5, 2, 26, 8, 27]. To realize this benefit of flexibility fully, the nonlinear mixing performed by different neurons must have sufficient diversity. The costs of this coding scheme, however, are twofold. First, generalization becomes more challenging because coding for each variable is not preserved as other variables change. Second, noise sensitivity must be considered: nonlinear mixed selectivity can be more susceptible to noise than

other coding schemes because modest changes in firing rates can correspond to very different encodings [51]. Note, however, that nonlinear mixing might also improve robustness to noise under certain circumstances, because the additional space between points enhances some (*e.g.*, discrete nearest neighbor) readouts [52].

How then is the dimensionality of the neural representations related to mixed selectivity? High dimensionality requires both nonlinear mixing and a diversity of neural responses. The dimensionality can be probed using either a classifier-based approach (the shattering dimensionality [2,8]) or more direct methods which are typically based on Principal Component Analysis [28–32]. Note that assessing whether an individual neuron has linear or nonlinear mixed selectivity depends on the choice of parameterization. For example, a neuron that has “mixed selectivity” because it responds to both reward size, and reward probability might be described as unmixed relative to action value. By contrast, the dimensionality of the population activity is independent of these choices. That is, the dimensionality is a property of a set of points (*i.e.*, the minimal number of coordinate axes needed to determine the position of all the points) and does not require any knowledge about the dependence of the activity on the task-relevant variables (parameters). Moreover, the response properties of individual neurons on their own are not sufficient to determine the dimensionality of the representation; the signal correlations between the responses across multiple cells are also important. For example, the nonlinear component of the response could be the same for every neuron in a population, and adding multiple cells with the same response component will not affect dimensionality at all. To return to our original example, consider a population in which neurons are modulated only by one particular combination of pitch and context (*i.e.*, the nonlinear component of the response is the same for every neuron). This lack of diversity across cells might prevent the representations from having the maximal dimensionality, and increasing the number of neurons will not help.

Insights from population activity: categorical vs. category-free encoding

A second way to identify interesting structure is to analyze the rows of the activity matrix. Each row is a vector containing the responses of an individual neuron to all the different experimental conditions. It can be represented as a point in the p -dimensional space as illustrated in Figure 2, on the right (p is the total number of conditions, which is the number of columns of the activity matrix). When the points corresponding to different neurons cluster together, it means that we will often encounter neurons with similar response properties (categorical representations). Category-free mixed selectivity means the converse that there are not discrete groups of neurons with particular combinations

of task dependence. Category-free populations suggest that the same population might be read out in multiple ways by downstream areas. When categories are found, this may suggest that neurons are dedicated to a particular function and are perhaps read-out in a largely static way by downstream areas. Interestingly, the observed categories might or might not line up with other ways of classifying neurons, such as morphology, physiology, gene expression, or projection patterns (for review, see Ref. [53]). If they do align, this could be a mechanism for allowing cells carrying specific information to play special roles in the circuit.

Both categorical and category-free representations can be low or high-dimensional (Figure 2, right). Interestingly, it is also possible to determine the dimensionality of the representations in the condition space: linear algebra dictates that the row rank of the matrix is the same as the column rank. However, in the categorical case, the number of clusters can limit the maximal dimensionality in the same way that the total number of points can. Note that the study of the distribution of points in the condition space depends less on experimenter choices than it does in many types of analysis. The only choice relevant to the dimensionality of the neural responses themselves is how trials are grouped into conditions, if at all.

An alternative way to characterize the structure in the condition space is to describe the neuronal responses using a linear encoding model, with each neuron's response modeled as a linear combination of task variables. The distribution of the coefficients is another way of visualizing clusters of neurons with similar responses (see Figure 2, rightmost column). If the encoding model includes only orthogonal variables and excludes nonlinear mixtures of variables, the coefficients' dimensionality will be less than or equal to the dimensionality assessed in either way described above.

Importantly, the categorical and category-free examples here represent the ends of what is likely a continuum. When faced with data that are intermediate, a reasonable next step is to consider specific hypotheses about the representations and apply a statistical test. One possible hypothesis is that there is a uniform distribution of values. This situation would correspond to a special type of category-free representation. To test this hypothesis, one can use the definition of random mixed selectivity and represent coding in a low-D coding space via dimensionality reduction, then test whether the distribution of coding vectors is random. For the latter step, numerous tests of uniformity on the hypersphere have been proposed (for review, see Ref. [33]). These include parametric (*e.g.*, Rayleigh test for von Mises–Fisher distributions [34,35] and Bingham test for antipodally symmetric distributions [36]); semi-parametric (*e.g.*, robust mixture models [37], Ajne test for concentration

in a hemisphere, and Giné test for axially symmetric distributions [34,35]); and non-parametric tests (*e.g.*, the general but low-powered random projections test [38], Projection Angle Index of Response Similarity (PAIRS) for clumpy distributions [6], and Elliptical Projection Angle Index of Response Similarity (ePAIRS) for clumpy elliptic distributions [39]; see also [40]). In all cases, however, statistical power quickly becomes limited when many dimensions of coding are considered. It is, therefore, important to accompany such tests with power analysis. If these tests are adequately powered but fail to find deviations from uniformity, this suggests that any categorical structure in the data is weak. If deviations are found, the next steps are challenging.

A number of practical challenges arise in determining whether categorical encoding is present in a population. Importantly, categorical representations are interesting when the number of categories (clusters in the condition space) is significantly smaller than the number of independent conditions. However, it is not clear how to estimate this number. For example, if we discretize a continuous stimulus variable, such as stimulus strength, the response of a neuron may be correlated across bins due to smoothness in the tuning curve. Conditions corresponding to two nearby values of the same variable would not be independent; therefore, the maximal number of clusters would be lower than naively expected. The maximal dimensionality is similarly affected by the independence of the conditions, making it difficult to assess whether neural representations are high-dimensional (*i.e.*, with a dimensionality close to maximal) or low-dimensional (*i.e.*, with a dimensionality that is much smaller than maximal) [41].

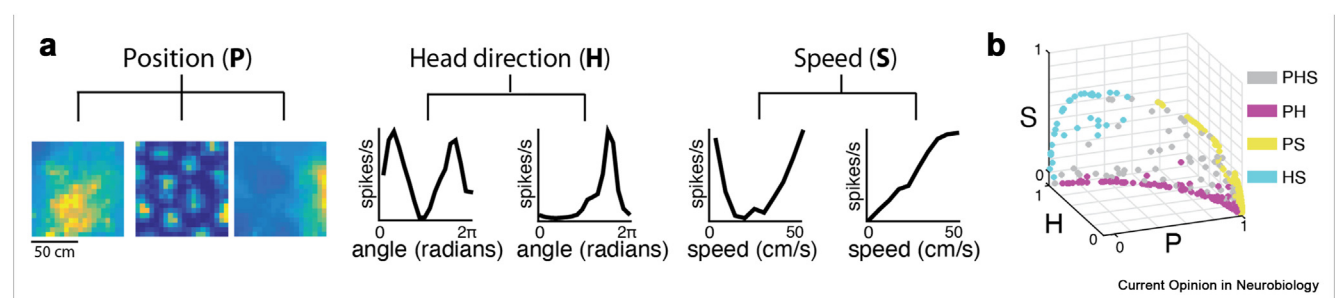
Recent literature examining mixed selectivity and categorical representations

In recent years, a number of papers have reported mixed selectivity for diverse task parameters across numerous brain areas. For example, a recent paper [42] focused on rat frontal cortex and value-based decisions. In this task,

rats were simultaneously presented with randomized auditory clicks, and visual flashes indicating reward probability and volume available at each side port. Upon training, rats reliably selected the side port with the greater subjective reward value. The team used clustering methods on a large population of single-unit recordings from the lateral OFC to interpret neural encoding of task variables (stimulus, reward attributes, reward outcome, reward history, and choice). Clear clustering was present, indicating the possible existence of categories of neurons, but the authors here went a step further to decode task variables from each cluster. Interestingly, all variables could be decoded from all clusters. This observation serves as a critical reminder that the existence of functional clusters of neurons does not mean the clusters correspond to individual task variables; even with clusters, there can be mixed selectivity. These kinds of recordings can be used to not only uncover whether mixed selectivity for the experimenter-defined task variables aligns with single neurons but also to test whether such mixing is linear or nonlinear, offering insight into the flexibility of the mixed representation for downstream readouts.

Mixed selectivity is not restricted to the cortex and has been observed for diverse variables in the hippocampus and medial entorhinal cortex (MEC) [43,7,44]. In MEC and hippocampus (dentate gyrus and CA1), neurons exhibit mixed selectivity for multiple navigational variables: spatial position, head direction, and running speed (Figure 3a). To explore the parameters encoded by each neuron with fewer assumptions about their tuning, a recent study [9] benefited from a more flexible statistical procedure (a nested linear-nonlinear-Poisson model fit to the spike train of each cell). As a result of this approach, the study was able to uncover mixed selectivity in many more cells than had been previously reported (Figure 3b). Interestingly, single-variable cells were still present in the population, demonstrating that mixed and single selectivity can co-exist within a single area and highlighting the need for analysis methods that

Figure 3



a Modulation of example neurons in medial entorhinal cortex by position (P), head direction (H), and speed (S). **(b)** Scatter plot showing modulation of neurons by P, H, and S. Colors indicate which two parameters modulated the neuron's activity, as determined by a flexible model. Cells modulated by all three parameters are gray.

allow for multiple types of encoding [37]. Importantly, if one discards all the cells that encode a particular variable (like place cells), it is still possible to decode position from the other cells [7]. The representations are typically highly distributed, and all neurons contribute to encoding each variable, whether their response properties are easily interpretable or not.

In the piriform cortex, recent work demonstrates that individual neurons not only reflect odor as previously known but unexpectedly also reflect spatial position [45]. Neural activity was measured while animals engaged in a spatial odor task in which odor cues could be presented at any arm of a 4-arm maze, and each odor served as an instruction to retrieve a reward at a particular location in world-centered coordinates. This configuration allowed the authors to determine the extent to which each piriform cortex neuron's activity was modulated by spatial position, odor, or both. Linear classifiers based on population activity were able to accurately decode either the animal's position or the odor, indicating that these are separable representations. More information about whether this mixed selectivity is linear or nonlinear would be helpful here, as this has important implications for neural coding as discussed above.

Another study, by contrast, explicitly tested for a categorical representation and concluded that individual neurons are categorically tuned for decision-related variables, such as confidence, integrated value, and reward size [39]. The authors studied rat orbitofrontal cortex during a task in which reward volume was manipulated in blocks and animals combined sensory and bias information to guide a choice. The authors first demonstrated that selectivity for task parameters was not random, but instead clustered, based on ePAIRS. ePAIRS is a modified version of the previously reported PAIRS test; ePAIRS is more conservative for detecting non-random mixing, while PAIRS is more conservative for identifying random mixing. In the case of rat orbitofrontal cortex, ePAIRS uncovered clear structure, suggesting that the mixing was not entirely random. The authors next identified putative clusters using spectral clustering methods [46,47] and tested that the identification of those clusters was stable. Finally, they used a Monte Carlo method with LASSO regression to further refine their understanding of the neural representation by determining that the clusters sparsely represented the task variables as they had defined them. One possible future direction for this work would be to determine whether all variables could be decoded from all clusters, despite their resemblance to individual variables, as discussed above (see also [2]).

Conclusion and outlook

Mixed selectivity has now been reported in diverse brain structures and contexts. A clear conclusion from these observations is that mixed selectivity is a common

property across both cortical and subcortical brain regions, and that mixing at the level of single neurons poses little problem for downstream areas that wish to decode a parameter of interest. Mixed selectivity, which is often observed to be very diverse across neurons, requires new tools for the analysis of neural data. Many of the new methods focus on the collective properties of populations of neurons, taking a perspective that is more similar to one of downstream readout neurons. Some of these methods are based on the computational properties of the representational geometry [2,8], and others like dPCA [48] and Targeted Dimensionality Reduction [49,50] allow the investigators to interpret the signals that are represented across multiple neurons, despite the large diversity of the neural responses. In addition to these methods, it is interesting to assess whether the representations are categorical or not. A categorical representation may indicate that there is an interesting structure to be investigated further.

What is less clear is how often mixed selectivity is nonlinear, potentially indicating a coding strategy that emphasizes readout flexibility. Moreover, it is not known how the transition from linear to nonlinear mixed selectivity occurs within a circuit, nor whether this is dependent on an animal's specific experience of behavioral needs. Causal experiments to test hypotheses about nonlinear mixed selectivity would also benefit the field and could have the power to demonstrate the hypothesized advantages of this coding strategy.

Conflict of interest statement

Nothing declared.

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