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Latent Variable Models Reconstruct Diversity of Neuronal Response to Drifting Gratings in Murine Visual Cortex

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ABSTRACT Decades of experimentation in visual neuroscience have been conducted with limited sample sizes of simultaneously recorded neurons. Past experiments have characterized the visual system based on statistical properties of individual neurons. Yet, no neuron functions in isolation: neural networks code information through their coordinated behavior. Calcium imaging can now simultaneously record larger populations than electrophysiological techniques could previously, allowing single-neuron analyses to be expanded to the network level. Larger datasets demand the development of computational approaches for network-level analysis. Our work validates a population modelling approach, utilizing two latent variable models and a large dataset of simultaneously recorded neurons. Rectified Latent Variable Model (RLVM) and Non-Negative Matrix Factorization (NNMF) were able to be fit to a large calcium imaging dataset without deconvolving the fluorescence signal into action potentials. These models show high reconstruction accuracy, with the RLVM outperforming NNMF. Both models’ reconstruction performance can be predicted via regression with node density and cell behavior metrics as predictors, showing that RLVM and NNMF are more effective on networks with high node density. Neurons and estimated latent variables show a spectrum of functional groups in response to simple stimulus features, with groups ranging from orientation and frequency specific, or orientation specific frequency agnostic, to orientation specific frequency modulated. Clustering of behavior profiles reveals some similar response profile groups between neurons and estimated latent variables in response to drifting gratings stimuli.

INDEX TERMS Rectified latent variable model, non-negative matrix factorization, autoencoder, drifting gratings, primary visual cortex.

I. INTRODUCTION
Repeated experimentation in visual neuroscience has found that neuronal activity in the primary visual cortex is responsive to specific local features of visual stimuli [1]–[4]. Cell-level neuronal behavior can be modelled as a combination of linear filters and nonlinear activation functions, arranged hierarchically. Cellular responses become more complex in higher visual areas, while remaining selective and responsive to specific features of visual stimuli. These properties accurately describe the behavior of a subset of the neurons in the visual cortex. However, the behavioral drivers of a majority of neurons are still to be proven [5]–[7].

This understanding of function in the primary visual cortex is the result of many independent studies focused on single-neuron analysis. However, it is clear that populations of neurons code information in ways that are not discernible from the activity of single neurons [8]. Reviews of neuroscience literature have come to the conclusion that standardized, high-throughput, experimentation is necessary in order to build computational models that can accurately describe the coordinated function of networks of neurons in the primary visual cortex [5]–[7]. Calcium imaging techniques allow for standardized experimental protocols that can simultaneously record hundreds of neurons [9].
While recording techniques advance, we must employ new computational methods to understand neuronal computation on the population-level. To extract as much information as possible from a limited sample size, it is logical to begin with a limited set of assumptions, and proceed with an empirical approach for information extraction. For this reason, interest in latent variable models in the field of neuroscience has been increasing, as these models deal directly with one of the most difficult hurdles in the field: experimental constraints only allow for an extreme sub-sample of neurons to be recorded simultaneously. Latent variable models are designed to deal with this exact problem - to extract hidden features driving the behavior of a network. Therefore, latent variable models designed specifically for neuronal networks should be excellent tools for investigating brain function. These models attempt to infer the unobservable inputs driving the behavior of observable neurons in the brain, such inferred inputs to the observed system are called latent variables (LVs). Questions remain whether such models are applicable to all regions of the brain equally, or which model is appropriate for certain circumstances. The work herein elucidates some of the advantages and limitations of two candidate latent variable models. A recently developed, biologically-plausible, Rectified Latent Variable Model (RLVM) was selected due to its specific design for application in neuronal networks [10]. We utilize a more simple, and well-studied model, Non-Negative Matrix Factorization (NNMF) as a comparator within the same analysis pipeline to give context and elucidate the advantages and limitations of the latent variable modelling approach.

Three observations are demonstrated herein. First, the Rectified Latent Variable Model (RLVM) and Non-Negative Matrix Factorization (NNMF) were able to be fit to a large calcium imaging dataset without deconvolving the fluorescence signal into action potentials. Both models achieve high reconstruction accuracy of neuronal behavior, with RLVM reconstruction performance greater than NNMF. This suggests that a common step (deconvolution from fluorescence to spikes) in the data processing pipeline of calcium imaging data may not be necessary. Second, both models’ reconstruction performance can be predicted via regression with cell behavior metrics as predictors. Third, not all the extracted latent variables (LVs) are highly correlated with individual features of the drifting gratings stimulus, but rather, the latent variables show diverse and complex tuning properties in response to the simple stimuli.

II. METHOD

A. CALCIUM IMAGING

This analysis utilizes 2-photon calcium imaging recordings from the murine primary visual cortex collected by the Allen Brain Institute [11]–[15]. The dataset analyzed here includes 249 recordings, with a total cell count of 25,115. Each recording includes anywhere from 21 to 461 neurons, and approximately thirty minutes of neuronal activity, during the presentation of the drifting gratings stimuli. Both latent variable models (RLVM and NNMF) were fit to each recording individually. The activity of each neuron is quantified by the filtered fluorescence trace at 30Hz [15]. Image preprocessing is performed by the Allen Institute as detailed in technical documentation; this analysis begins with the neuropil-corrected fluorescence trace for each cell [12], [14], [15]. Fluorescence traces were filtered with a third-order Savitsky-Golay filter with a 1.33-second window, via the MATLAB function sgolayfilt, as utilized in [10]. Each filtered fluorescence trace was then z-normalized to obtain traces with mean of zero and standard deviation of 1. Normalized traces were then shifted up by the absolute value of the lowest value of cell activation for the recording so that all cell activation levels were non-negative. Recordings were obtained from six sub-regions of the murine primary visual cortex. Description of recording locations can be found in [12]. Recordings were downloaded in August 2020, with Experiment ID ranging from 511498742 to 716655272. After obtaining the required calcium imaging recordings, cells were selected for analysis via two requirements. First, they must have a signal-to-noise ratio greater than one. Second, they must have a preference for the drifting gratings stimulus over other stimuli in the recording. Cells determined to be statistically significantly responsive to the drifting gratings stimulus at a p-value less than 0.05 were included. Finally, only recordings with greater than 20 cells after this selection process were included. From an originally-mined dataset of 424 recordings, and a total of > 45,000 neurons, this criteria excluded 175 recordings and > 20,000 neurons. This resulted in a total of 25,115 modelled neurons from 249 recordings. Distributions of cell counts per recording can be found in Fig. 1. These strict criteria were used to focus solely on the most well-studied dynamic stimulus: drifting gratings. All other time periods during the experimental recordings were removed before the latent variable models were fit to the neuronal behavior. The selected data were then used to fit the latent variable models to each experiment individually.

B. RECTIFIED LATENT VARIABLE MODEL

The Rectified Latent Variable Model (RLVM) was developed as a biologically-plausible model for neuroscientific investigation [10]. This model is effectively a single-layer
autoencoder with a rectified linear activation function. It has two main characteristics that separate it from other common dimensionality reduction techniques: 1) the estimated latent variables are non-negative, and 2) they can be correlated. Whiteway previously applied this model to a behavioral task, with recordings from the rat barrel cortex [10]. The previous application to calcium imaging recordings deconvolved the df/dt calcium traces into spike-rates before fitting the RLVM. The analysis herein evaluates the effectiveness of the RLVM in a different species and cortical region.

RLVM is formulated in [10]:
\[
\hat{y}_t = f(Wg(Wx_t + b) + b)
\]
(1)

where \(\hat{y}_t\) is the neural activity, \(f(.)\) is a linear function of the weights \(W\) and biases \((b)\) relating the latent variables \(x_i\) with the neural activity \(\hat{y}_t\). Equation (2) shows the defining feature of the RLVM: the rectification of the estimated latent variables. Instead of optimizing non-negative latent variables \(z^t\), the RLVM estimates unconstrained latent variables \(x^t\), then passes them through a rectified linear function \(g(.)\):
\[
z^t_i = g(x^t_i) = \begin{cases} 
0 & \text{if } x^t_i \leq 0 \\
x^t_i & \text{if } x^t_i > 0
\end{cases}
\]
(2)

We validated that the RLVM can be fit to calcium traces without deconvolution. For each experiment, the RLVM was fit to the behavior of the selected cells only during the presentation of the drifting gratings stimulus. This was approximately 30 minutes of recording time for each experiment. One RLVM was fit per recording session, resulting in 249 RLVM fittings. For each experiment, the number of latent variables was constant at 10. Each fitting included two types of cross-validation: five-fold cross validation, and single-leave-one-out (SLOO), as described in [10]. In SLOO validation, the cell activity was predicted via a leave-one-out procedure wherein the latent variables were estimated without the left-out cell. These latent variables were then used to predict the cell behavior of the left-out cell. This was repeated for each cell, to produce a prediction accuracy measurement quantified as the Pearson correlation \((R^2)\) between the actual and predicted cell behavior. Distribution of prediction accuracy for all of the 25,115 cells is plotted in Fig. 2.

Previous analysis evaluated the effect of the number of latent variables on the accuracy of model prediction [16]. This analysis found that there is a ceiling for the number of latent variables at which the RLVM will no longer compress neuronal data, and instead model neuronal activity on a one-to-one basis. Therefore, it is known that the proportion of latent variables to neurons must be relatively low for the RLVM to provide insight. Along with the previous analysis, a preliminary analysis on this specific dataset was conducted, and found that the model reconstruction accuracy plateaued for a majority of recordings when the model includes 10 latent variables. This is in line with the concept that Neural Task Complexity governs the underlying latent structure of neuronal behavior, independently of the number of recorded neurons [17]. Based on the performance plateau, we chose to fit all recordings with 10 latent variables. Considering that the number of latent variables should be much lower than the number of modelled neurons, after setting the number of latent variables, we excluded any recordings with less than 21 candidate neurons. This results in a range of compression factors from 2 to 46, with 60% of recordings between 2 and 8 times compression.

After fitting RLVM with 10 latent variables to each experiment, the reconstruction performance of the model was quantified as the Pearson correlation \((R^2)\) between the observed and reconstructed traces via two testing methods: five-fold cross-validation in the time domain (CV), and single-leave-one-out (SLOO). SLOO testing was performed as described by Whiteway [10]. Firstly, the RLVM is fit to the entire recording (all cells at all time points of a single recording session). Then, the encoding weights from one cell to all latent variables are set to zero, and the latent variables are estimated from the remaining cells’ activities. The estimated latent variables are then used to reconstruct the left-out cell’s activity. The process is repeated until each cell has been ‘left out’ and reconstructed in this manner. SLOO testing results in lower reconstruction performance if a single cell disproportionately drives the activity of many latent variables in the trained model [10]. The distribution of reconstruction accuracy for both the RLVM and NNMF models under both testing schemes is plotted in Fig. 2.

C. NON-NEGATIVE MATRIX FACTORIZATION

RLVM was chosen as a biologically-plausible model that utilizes few a-priori assumptions. The model was proposed as a method to reveal insights into the function of neurological systems. We asked the question – could the insights gained from the RLVM be obtained from a more simple model? Non-Negative Matrix Factorization (NNMF) is a common
tool that has similar assumptions as RLVM. Namely, NNMF estimates non-negative factors that drive the activity of the recorded time-series data, with no assumption of orthogonality in the latent factors [18]. This model was evaluated in parallel to the RLVM as a more computationally-efficient model with similar assumptions. NNMF was put through the same pipeline of fitting and analysis as RLVM: NNMF was fit to each experiment individually, and model prediction accuracy was quantified via Pearson correlation ($R^2$) between the observed and predicted cell behavior under two testing schemes, as described in the previous section. Fig. 2 presents the distribution of prediction accuracy of all 25,115 neurons in this analysis.

The NNMF decomposition is described in (3):

$$A = WH$$ (3)

where the NNMF factors the non-negative matrix $A$ into non-negative factors $W$ and $H$. In this case, $A$ is the neuronal activation matrix, $W$ is the weight matrix and $H$ is the latent variable matrix [18].

The factors $W$ and $H$ are chosen to minimize the root-mean-squared residual $D$ between $A$ and $WH$:

$$D = \frac{\text{norm}(A - WH)}{\sqrt{nm}}$$ (4)

where $n$ is the number of neurons (number of rows in $A$), and $m$ is the number of time points (number of columns in $A$).

NNMF utilizes an iterative approach that begins with random initial values for $W$ and $H$. Because the iterative approach may result in root-mean-squared residual $D$ that arrive at local minima, repeated factorizations are performed with independent random initializations. The norm(.) term in (4) is the Frobenius norm, as defined by:

$$\|X\|_F = \sqrt{\sum_{i=1}^{m} \sum_{j=1}^{n} |a_{ij}|^2} = \sqrt{\text{trace}(X^T X)}$$ (5)

D. RECONSTRUCTION OF CELL TUNING PREFERENCES

The drifting gratings stimulus lends itself to a number of metrics for quantifying the response properties of the recorded neurons. The Allen Institute provides behavioral metrics for each recorded cell. For example, the preferred stimulus frequency and preferred stimulus orientation for each cell. To investigate the RLVM and NNMF reproduction of the network tuning properties, the distribution of preferred frequency and orientation across all analyzed cells are shown in Figs. 3 and 4.

For each recording, the preferred frequency and orientation of each cell is provided by the Allen Institute. After reconstructing the recorded neuronal activity with the Latent Variable models, the preferred stimulus is recomputed and a histogram is produced for each recording. Figs. 3 and 4 show the average distributions of frequency and orientation tuning across all reconstructed recordings, with error bars corresponding to standard deviation across recordings.

E. FACTORS AFFECTING MODEL RECONSTRUCTION ACCURACY

We previously found that the RLVM model achieves higher reconstruction accuracy when the node density is greater [16]. Node density is a simple graph-theoretic measure of how tightly two nodes in a graph are connected. In the single-neuron recording case, node density is the correlation between two simultaneously recorded neurons. For each recording, the pairwise Pearson correlation was computed for all the neurons in the recording. This forms a weight matrix that is a graph-theoretic quantification of the network. The absolute value of this matrix is taken to represent a weighted, undirected, graph. The average weight for each cell is the cell’s node density. Figs. 5 and 6, illustrate the relationship between RLVM/NNMF reconstruction accuracy and node density per cell. These scatter plots show one point for each of the 25,115 cells in this analysis, with the cell’s node density on the x-axis, and the respective latent variable model cross-validation (CV) reconstruction performance on...
A linear regression model was then fit to predict the LV model reconstruction accuracy from the eight cell behavioral metrics (and node density). LASSO regression was used to identify significant predictors of latent variable model performance. Node density was identified as the dominant predictor of model reconstruction accuracy. Cell behavior metrics of direction selectivity, response reliability, orientation selectivity, and temporal frequency discrimination, were also determined to be significant predictors. Interactions-effects models utilizing the identified predictors were fit to predict the latent variable model reconstruction accuracy, but showed negligible performance increase with a disproportionate increase in model complexity. Interactions models increased regression performance by 0.01 with $15 - 18$ coefficients for each regression model. Only linear results are reported herein.

The linear models relating cell metrics to cross-validated RLVM and NNMF reconstruction accuracy respectively, are described in (6) and (7). Significant predictors were: node density ($x_d$), direction selectivity ($x_{ds}$), response reliability ($x_r$), orientation selectivity ($x_{os}$), and temporal frequency discrimination index ($x_{fd}$), with the response $\hat{y}$ being the reconstruction accuracy of the respective latent variable model. Fig. 7 shows the performance of the regression models, with the corresponding coefficients plotted in Fig. 8.

$$
\hat{y}_{RLVM} = 0.092x_d - 0.016x_{ds} + 0.008x_r - 0.008x_{os} + 0.003x_{fd} + 0.793 \quad (6)
$$

$$
\hat{y}_{NNMF} = 0.15x_d - 0.015x_{ds} - 0.015x_r - 0.017x_{os} + 0.010x_{fd} + 0.64 \quad (7)
$$

F. LATENT VARIABLE RESPONSE PROFILES TO DRIFTING GRATINGS

To visualize the neuronal response to drifting gratings stimuli, we utilized star plots similar to [13], with stimulus conditions in polar coordinates and the size of points corresponding to evoked response (Fig. 9). In polar coordinates, the angle corresponds to the orientation of the drifting gratings stimulus, while the radius corresponds with frequency of the stimulus. We show increased absolute value of evoked response via increased size of the dot at each vertex. Positive responses are in red and negative responses are in blue. Each star plot is adjusted by a scalar so that the largest dot is the same size across all plots. Fig. 9 contains star plots for ten cells and ten latent variables from each latent variable model.

The evoked response of the latent variable to the stimulus presentation is quantified in the same manner as the Allen Institute quantified neuronal responses [13]. The mean fluorescence of the cell (or the value of the latent variable) during the 1-second preceding stimulus presentation was used as a baseline. The evoked response is defined as the difference between the mean value during stimulus presentation and the baseline, divided by the baseline. Equation (8) demonstrates this metric; where $F$ is the average cell fluorescence (or latent variable value) during stimulus presentation and $F_0$ is the...
FIGURE 7. Regression performance: cell behavioral metrics and node density can predict RLVM and NNMF reconstruction accuracy. Regression model includes six predictors of RLVM and NNMF reconstruction accuracy on two types of test holdouts: traditional cross-validation (CV) and single-leave-one-out (SLOO).

FIGURE 8. Regression coefficients: coefficients for the linear model. All estimated coefficients are highly significant, $p < 0.0001$. Node density is the strongest predictor for the performance of both latent variable models tested herein.

baseline value. Each stimulus condition appears 15 times in a recording session, with each trial preceded by 1-second of inter-stimulus gray presentation. The star plots indicate the average response of the respective cell - or latent variable - across all 15 trials. The preferred stimulus condition for each respective cell - or latent variable - is defined as the stimulus with the greatest evoked response.

$$\textit{EvokedResponse} = \frac{F - F_o}{F_o} \quad (8)$$

G. CLUSTERING OF STIMULUS EVOKED RESPONSE

After computing the evoked response, we clustered cells based on their tuning behavior via k-means clustering. After clustering with $k = 20$, the clusters were ordered based on their size (the number of cells in each cluster). The ten largest clusters account for 60% of the cell population. We then similarly clustered the latent variables from RLVM and NNMF into 20 groups, respectively. Fig. 9 (left) illustrates the cell and latent variable star plots that are closest to the cluster centroids. The left column of star plots shows the cell star plots ordered by cluster size from largest at top. RLVM and NNMF star plots are ordered by visual similarity to the cell star plots. Fig. 9 (right) shows the percentage of cells or latent variables in each cluster.

We investigated the optimal $k$, evaluating the clustering with groups sized $2 - 100$, the mean square distance from cluster centroid was found to plateau at 30 groups. However, with any $k > 20$, we observed that the cluster centroids were less visually distinct. Furthermore, when the RLVM latent variables were clustered, the mean square distance from cluster centroid was found to plateau at 20 groups. The ten largest cell clusters represent a majority of the cells, therefore...
ten centroid star plots are used to visualize the cell and latent variable behavioral groups.

III. RESULTS

A. LATENT VARIABLE MODELS RECONSTRUCT CELL ACTIVATION WITHOUT DECONVOLUTION

Both RLVM and NNMF are able to be fit, with model convergence. The model accuracy, as quantified by the Pearson correlation ($R^2$) between the predicted and observed cell behavior is shown in Fig. 2. This figure shows the distribution of model prediction on two types of cross-validation test data for all 25, 115 neurons in the 249 analyzed recordings. Fig. 2 shows that the distribution of RLVM reconstruction accuracy is skewed to the left, while NNMF reconstruction accuracy has a more uniform distribution. RLVM achieves reconstruction accuracy greater than 0.8 $R^2$ in 57% and 44% of cells as quantified by time cross-validation and SLOO testing, respectively. NNMF achieves lower reconstruction accuracy rates with 28% and 16% of cells reconstructed above 0.8 $R^2$ per validation method, respectively.

These results show that both RLVM and NNMF can predict the cell behavior of neurons in the visual cortex without deconvolution. In this case, these models are fit to, and predicting the calcium level inside each cell with minimal filtering from the raw fluorescence trace. With the same number of latent variables, RLVM achieves higher prediction accuracy than NNMF. It is expected that the RLVM would perform better, as RLVM has more terms that allow the model to describe complex neuronal activation patterns.

B. RECONSTRUCTION OF CELL TUNING PREFERENCE DISTRIBUTION

After the cellular-level reconstruction, the population-level distribution of cell tuning preferences is an important observation in the drifting gratings experiment. Figs. 3 and 4 show that the model-reconstructed cellular activation reproduces the distribution of cell tuning preferences. The reconstructed cellular activity from both models results in tuning preference distributions that are not statistically different from the observed cellular preferences ($p > 0.1$). Both RLVM and NNMF cell tuning preference distributions mimic the distribution of the observed cell activity.

Fig. 3 shows that the slowest frequency (1Hz) is the preferred frequency for a greater number cells than any other frequency, with 42% of cells preferring 1Hz. Fewer percentages of cells prefer each frequency as the frequency increases, with approximately 17 – 11% of cells preferring each of the frequencies 2Hz-15Hz, respectively. Both LV models follow this same distribution, with a majority of the cells preferring the slower frequencies. However, the reconstructed cellular behavior from both LV models skews this distribution slightly more to the right, with NNMF reconstruction showing the greatest percentage of preference for slower frequencies.

The distribution of cell preference for orientation (Fig. 4) is more uniform than cell preference for frequencies. Observed cell preference is for vertical bars (0° and 180°), with the lowest percentage of cells preferring the stimulus at 135° and 315°. For reference, 0° and 180° are vertical bars that appear to move towards the right and left, respectively. The bars of 135° and 315° stimuli are angled diagonally approximately from top left to bottom right (or 11 to 5 on the clock), with 135° appearing to move top-right to bottom-left and 315° moving bottom-left to top-right. Again, both LV models mimic this same distribution of cell tuning preference, but further exaggerate the distribution of cells with preference for the vertical bars, with NNMF reconstruction showing the greatest number of cells with preference for vertical bars.

C. FACTORS AFFECTING MODEL RECONSTRUCTION ACCURACY

Both RLVM and NNMF show a wide range of reconstruction accuracy per cell, and there are certain factors related to this range. Node density correlates with both RLVM and NNMF reconstruction performance. Using regression modelling, we have determined that four cell behavior metrics are minor predictors of reconstruction accuracy in RLVM and NNMF.

1) NODE DENSITY CORRELATES WITH LV MODEL RECONSTRUCTION ACCURACY

As shown in previous work, RLVM reconstruction accuracy is correlated with node density [16]. NNMF also demonstrates this behavior, with node density correlated to NNMF reconstruction accuracy at a slightly greater degree than the RLVM reconstruction accuracy. Figs. 5 and 6 show a clear lower-bound in the relationship between LV model reconstruction performance and the node density. When compared to RLVM, NNMF’s more uniform distribution of reconstruction accuracy is illustrated by the range of points along the y-axis of Fig. 6.

2) CELL BEHAVIOR METRICS ARE PREDICTORS OF LATENT VARIABLE MODEL ACCURACY

Results of regularized linear regression show that a five-factors model can capture the reconstruction performance of both latent variable models. Model fits all exceed 0.64 Pearson correlation ($R^2$) between observed and predicted latent variable model fit, with the RLVM SLOO reconstruction performance most accurately modelled at 0.79$R^2$. Node density is the dominant predictor of RLVM and NNMF reconstruction accuracy, while four behavioral metrics are minor predictors.

Regression coefficients show that the node density is the strongest predictor of RLVM reconstruction accuracy. Although direction and orientation selectivity, response reliability, and frequency discrimination are found to be significant predictors ($p < 0.001$), their respective coefficient values have much smaller absolute values than the regression coefficient for Node Density.

Coefficients of the regression model predicting NNMF reconstruction performance from the cell behavior metrics...
show that NNMF performance is also related to a cell’s node density. NNMF reconstruction performance is related to each of the same cell behavior metrics as the RLVM performance. However, NNMF reconstruction accuracy is more highly correlated with node density than RLVM reconstruction accuracy, and this is reflected in both the regression model coefficients as well as the pairwise correlations.

**D. CELLS AND LATENT VARIABLES DEMONSTRATE DIVERSE TUNING PROPERTIES**

Star plots in Fig. 9 illustrate the diversity of cell behavior, and extracted latent variables, in response to the drifting gratings stimulus. After k-means clustering with \( k = 20 \), we found the ten largest clusters account for 60% of the cell population, and demonstrate varied behavior profiles in response to the drifting gratings stimulus. Fig. 9 (left) illustrates the cell and latent variable star plots that are closest to the cluster centroids. The left column of star plots shows the cell star plots ordered by cluster size from largest at the top. RLVM and NNMF star plots are ordered by visual similarity to the cell star plots, with corresponding cluster sizes on the right. The ten largest clusters of cell evoked responses represent 60% of the total population, with the plotted clusters of RLVM and NNMF accounting for 53%, and 51% of their respective populations. Therefore, these star plots illustrate exemplars that represent the majority of the cell (and latent variable) behavior profiles.

These exemplars show diverse and complex behavior profiles in response to the drifting gratings stimulus. Along with the expected cell response profiles that are both frequency and orientation selective (rows 6 – 8), exemplars show that many cells are orientation selective and modulated by frequency (as in rows 1, 3, 10), or only frequency selective (rows 4 and 5). Rows 2 and 8 show opposing, but uniform response profiles, with row 2 excited by all stimulus conditions, and row 8 consistently inhibited by all stimulus conditions. The latent variables estimated by both RLVM and NNMF have cluster exemplars that mimic each of the various exemplar cell response profiles, with one clear discrepancy: latent variable clustering did not find clusters that are distinctly orientation and frequency selective. While cell clusters 6 – 8 show behavior profiles that are distinctly selective for particular orientations, with slight modulation by frequency, latent variable clusters did not demonstrate such distinct selectivity for a single stimulus.

**IV. DISCUSSION**

Latent variable models are powerful, popular, tools for extracting information from sub-sampled data [19], [20]. Latent variable models with non-negativity constraints are utilized across a diverse range of applications including, but not limited to, genomics [21], sound source separation [22], and brain-computer interface [23]. Our work has three main contributions: first, we show that two common latent variable models are able to fit calcium imaging data from the mouse visual cortex without the use of deconvolution. Second, node density and cell behavior metrics affect latent variable model performance. Third, extracted latent variables mimic the diverse response profiles that murine V1 cells exhibit in response to drifting gratings stimulus.

**A. NODE DENSITY AFFECTS LATENT VARIABLE MODEL RECONSTRUCTION ACCURACY**

Our previous work showed a relationship between the RLVM reconstruction accuracy and the node density of a neuron in its network [16]. We investigate this further by correlating more cell behavior metrics with RLVM and NNMF reconstruction accuracy. We found that both RLVM and NNMF reconstruction accuracy are correlated with increasing node density, and that, of the nine factors tested herein, the node density is the greatest individual predictor of latent variable model reconstruction accuracy. We also analyzed interactions effects, but they did not appreciably increase the regression fit. Both RLVM and NNMF perform better when the modelled network is dense. This insight can be utilized during model selection, as network density is a simple computation that can be performed prior to fitting these models. If the network is dense, it is more likely that these models will perform well. LASSO regression also shows four cell behavior metrics are statistically significant \((p < 0.0001)\) predictors of RLVM and NNMF reconstruction performance: direction and orientation selectivity, response reliability, and frequency discrimination. Each of these behavior metrics correspond with the cell’s ability to discriminate between different drifting gratings conditions, as opposed to other metrics we tested such as \( \text{response~p-value} \) that track a cell’s response the drifting gratings as a whole in comparison other stimuli in the experimental recording. Although statistically significant, these behavior predictors are minor in comparison to the dominant predictor: node density. Node density is a computationally efficient measure that can be used to quantify relationships in multivariate time-series data across applications, making this finding useful for model selection in the diverse fields utilizing NNMF.

**B. CELLS AND LATENT VARIABLES DEMONSTRATE DIVERSE TUNING PROPERTIES**

V1 cell behavior is typically quantified and presented via two-dimensional tuning curves, with only positive components. Fig. 9, illustrates that cells exhibit diverse and complex tuning properties that are not easily captured with two-dimensional visualizations. The cell response profiles can be clustered into numerous behavioral groups, while the latent variables extracted via RLVM and NNMF also exhibit a similar range of response profiles. Not only are many units responding preferentially for a single stimulus feature: orientation and frequency independently, but also specific combinations of these features such as in the first row of Fig. 9 where cells are orientation selective and frequency modulated. We can also see that some units are inhibited from a baseline activation level during the presentation of the drifting gratings.

The questions raised from this analysis suggest that there may be many more factors, and more highly complex
representations, in the lower visual system than has been previously explored. By limiting the a-priori assumptions surrounding the most common experiments conducted in the visual system, the RLVM and NNMF illustrate a high diversity of information carried by the visual system at the lowest levels. Previous studies have suggested that there are many possible influences for the behavior of cortical neurons that may or may not be observable in experimental contexts. For example, cell behavior may be influenced by a wide range of factors such as pupil dilation, motor output, local field potentials, dopamine release, or population rate [24]–[28]. We utilized regression modelling to test the available metrics in this dataset for their relationship with latent variable model reconstruction, and found node density to be the dominant predictor of RLVM and NNMF reconstruction.

Decades of research in visual neuroscience has lead to a view that neurons in the primary visual cortex are responsive to specific stimulus features. This view purports a hierarchical network structure where neurons in the latter parts of the system respond to increasingly complex stimulus features. Due to experimental constraints, these studies have focused on the behavior of individual neurons, not on populations of neurons simultaneously. Through calcium imaging, the Allen Institute has created a high-quality, high-throughput, assay. It is now possible to test whether the historical conclusions derived from single-cell analyses are consistent with the population-level dynamics. Utilizing this new experimental dataset requires validation of new computational approaches. Latent variable models are powerful tools for inferring the unobservable inputs driving the behavior of observable neurons in the brain. When applying these models to the modern population-level recordings from the Allen Institute, the historical view - that neurons in the primary visual cortex are primarily responsive to stimulus features - is augmented by these results showing non-gaussian response profiles to drifting gratings stimulus. Both cells and estimated latent variables demonstrate complex tuning properties in response to the simple stimulus, with a majority of neurons clustering into groups with a range of response profiles.

V. CONCLUSION
Two latent variable models, a biologically-plausible Rectified Latent Variable Model (RLVM), and Non-Negative Matrix Factorization (NNMF), can be used to model calcium traces of populations of neurons in the visual cortex, without deconvolving calcium imaging data into spike representations. Both models demonstrate high performance when reconstructing neuronal behavior in the primary visual cortex, with RLVM outperforming NNMF on reconstruction accuracy. Similarly, both models reconstruct the distribution of cell stimulus preference across the network, with RLVM again reconstructing cell tuning preference more accurately than NNMF. It is evident that these models perform better in networks with high density. Linear regression shows that RLVM and NNMF reconstruction may also be affected by the consistency of cell response to stimuli, but the behavior metrics tested herein have a minor effect compared to the dominant predictor: network density. The latent variables estimated via RLVM and NNMF mimic the response profiles of the recorded neurons, with consistent behavioral groups similar to the cellular response profiles. Clustering of evoked response profiles reveals that both cells and latent variables demonstrate a variety of profiles along a spectrum of sensitivity to either stimulus frequency or orientation, or combinations of both stimulus features. For example, not only are there groups of cells responsive to a single combination of frequency and orientation, but there are groups of cells demonstrating orientation selectivity with frequency modulation, and groups showing single feature discrimination such as orientation selectivity regardless of frequency. Instead of forming clusters with distinct response profiles in comparison to the neuronal behavior, the RLVM and NNMF both estimate latent variables that have similar response profiles to the cellular behavior.

Latent variable models are an enticing species of model for neuroscience, as they are specifically designed to deal with one of the main difficulties inherent in experimental neuroscience - maximizing information extraction from subsampled populations. Both RLVM and NNMF can be used to model populations of neurons in the murine visual cortex, where RLVM offers a higher reconstruction accuracy than NNMF with a small set of latent variables. These models achieve higher reconstruction performance when applied to dense networks. The response profiles of the latent variables can be grouped into similar clusters as neuronal behavioral profiles in response to the drifting gratings stimulus.

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REFERENCES


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