over
Title: Real-Time Bayesian Optimization for Efficient Multidimensional Neural Tuning Characterization

Authors: P. Wu, A. Shankar, A. Chiu, M. Shahab, C. Burgess, E. Savier, A. Draelos

Summary (300 words):
A fundamental goal in neuroscience is understanding the relationship between sensory stimuli and resultant neural responses. Characterizing neural responses across multiple dimensions of visual stimuli - such as direction of motion, size, and contrast - is essential for understanding complex sensory processing and tuning. As we move towards studying real-world conditions, a challenge arises from the large number of stimuli to present when forming all possible combinations of these parameters, along with time and financial constraints posed by in vivo experiments. There is thus a critical need for systems capable of efficiently capturing neural responses in real time and adaptively selecting a manageable subset of stimuli to display. These systems must also be flexible enough to learn and identify neural tuning curves across various experimental platforms, brain regions, behavioral conditions, and visual inputs. Here, we developed an efficient closed-loop system that integrates streaming modeling with experimental imaging to capture and analyze neural responses in high-dimensional stimuli environments in vivo. We employed Bayesian optimization with Gaussian Processes and custom multidimensional kernels to fit multivariate tuning curves and thereby identify stimuli that maximize neural responses. We applied our method to study the mouse primary visual cortex (V1), using two calcium indicators (GCaMP6s,6f) and five C57BL/6 mice. We successfully characterized multidimensional neural responses across a five-dimensional visual space, adaptively sampling fewer than 91 stimuli (about 3% of ~3k possibilities). Preliminary results revealed distinct functional types of neuron preferences. For example, the directional tuning of some V1 neurons is modulated simultaneously by stimulus size and contrast; interactions that would have been missed if such combinations of stimulus dimensions were not measured. With efficient real-time identification of neural tuning preference in vivo, we can also improve robustness to noise and dynamic changes in neural tuning through optimizing kernel selection and hyperparameter tuning throughout an experiment.

A fundamental goal in neuroscience is understanding the relationship between sensory stimuli and resultant neural responses. Characterizing neural responses across multiple dimensions of visual stimuli - such as direction of motion, size, and contrast - is essential for understanding complex sensory processing and tuning. As we move towards studying real-world conditions, a challenge arises from the large number of stimuli to present when forming all possible combinations of these parameters, along with time and financial constraints posed by in vivo experiments. There is thus a critical need for systems capable of efficiently capturing neural responses in real time and adaptively selecting a manageable subset of stimuli to display. These systems must also be flexible enough to learn and identify neural tuning curves across various experimental platforms, brain regions, behavioral conditions, and visual inputs. Here, we developed an efficient closed-loop system that integrates streaming modeling with experimental imaging to capture and analyze neural responses in high-dimensional stimuli environments in

vivo. We employed Bayesian optimization with Gaussian Processes and custom multidimensional kernels to fit multivariate tuning curves and thereby identify stimuli that maximize neural responses. We applied our method to study the mouse primary visual cortex (V1), using two calcium indicators (GCaMP6s,6f) and five C57BL/6 mice. We successfully characterized multidimensional neural responses across a five-dimensional visual space, adaptively sampling fewer than 91 stimuli (about 3% of ~3k possibilities). Preliminary results revealed distinct functional types of neuron preferences. For example, the directional tuning of some V1 neurons is modulated simultaneously by stimulus size and contrast; interactions that would have been missed if such combinations of stimulus dimensions were not measured. With efficient real-time identification of neural tuning preference in vivo, we can also improve robustness to noise and dynamic changes in neural tuning through optimizing kernel selection and hyperparameter tuning in real time.

A fundamental goal in neuroscience is understanding the relationship between sensory stimuli and resultant neural responses. Characterizing neural responses across multiple dimensions of visual stimuli - such as direction of motion, size, and contrast - is essential for understanding complex sensory processing and tuning. As we move towards studying real-world conditions, a challenge arises from the large number of stimuli to present when forming all possible combinations of these parameters, along with time and financial constraints posed by *in vivo* experiments. There is thus a critical need for systems capable of efficiently capturing neural responses in real time and adaptively selecting a manageable subset of stimuli to display. These systems must also be flexible enough to learn and identify neural tuning curves across various experimental platforms, brain regions, behavioral conditions, and visual inputs. Here, we developed an efficient closed-loop system that integrates streaming modeling with experimental imaging to capture and analyze neural responses in high-dimensional stimuli environments *in vivo*. We employed Bayesian optimization with Gaussian Processes and custom multidimensional kernels to fit multivariate tuning curves and thereby identify stimuli that maximize neural responses. We applied our method to study the mouse primary visual cortex (V1), using two calcium indicators (GCaMP6s,6f) and five C57BL/6 mice. We successfully characterized multidimensional neural responses across a five-dimensional visual space, adaptively sampling fewer than 91 stimuli (about 3% of ~3k possibilities). Preliminary results revealed distinct functional types of neuron preferences. For example, the directional tuning of some V1 neurons is modulated simultaneously by stimulus size and contrast; interactions that would have been missed if such combinations of stimulus dimensions were not measured. With efficient real-time identification of neural tuning preference *in vivo*, we can also improve robustness to noise and dynamic changes in neural tuning through optimizing kernel selection and hyperparameter tuning in real time.

Additional details:
Significance: Neurons respond to and encode information from complex, high-dimensional stimuli. However, most current approaches to elicit these responses rely on non-adaptive methods: pre-selected, 1 or 2 dimensional, often randomly-ordered stimuli are used, and tuning properties are analyzed post-hoc [3]. Such methods are intractable for higher-dimensional

stimuli, as even a three-dimensional stimulus space with ten values per dimension yields $10^3 = 1000$ unique combinations. While previous studies have explored high-dimensional stimuli using natural images from ImageNet [4,5], these stimuli are difficult to parameterize, making it challenging to disentangle the specific contribution of each feature. Our work addresses this limitation by developing and validating a closed-loop computational approach for measuring multidimensional responses in the mouse visual cortex. This system leverages Bayesian optimization with Gaussian processes to dynamically model the relationship between neural responses and stimuli, enabling the efficient characterization of peak tuning in a 5-D stimulus space. We build on top of *improv* [6], a software platform that executes adaptive experimental workflows, and: (1) create two new interfaces to acquire streaming images from commonly-used 2-photon microscopy data acquisition softwares (Bruker PrairieView and Scanbox); and (2) measure neural responses to 5D stimuli (Fig. 1a) with high granularity from the mouse V1. To our knowledge, this work represents the first demonstration of a closed-loop system with customizable, high-dimensional parametric stimuli in mice.

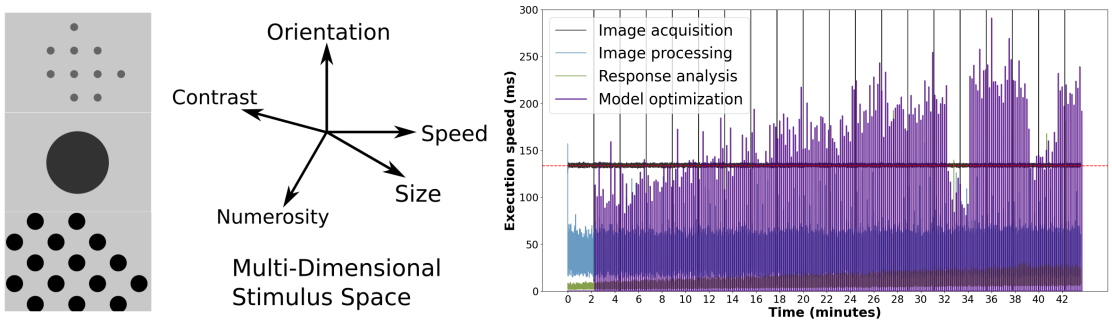

Figure 1: System specification & performance speed

Methods: We constructed an experiment using the *improv* software platform [6], integrating the CaImAn algorithm [7] for online analysis of calcium fluorescence images. We modified the pandastim library [8] for generating visual stimuli to include 5 stimulus parameters (orientation, speed, size, number of circular stimuli, contrast), and incorporated our Bayesian inference methods for finding the optimal next stimulus. We acquired images from Scanbox and Bruker microscopes using custom MATLAB modules and Python code that leveraged the ZeroMQ library for inter-computer communication, and developed methods to adapt to variations in image size and multiplexing. *In vivo* testing demonstrated that our system can operate stably at the 7.5 Hz data acquisition rate to analyze 500 neurons at once (Fig. 1b).

We then modeled the tuning properties of individual neurons and identified the stimulus that elicited peak responses. We used a Gaussian Process (GP) to model a single neuron's multidimensional tuning curve. $f(\boldsymbol{x}) \sim GP(m(\boldsymbol{x}), k(\boldsymbol{x}, \boldsymbol{x'}))$, where m is the mean function. Here, the kernel k captures the assumed similarity between stimuli, providing a structured stimulus-response map. We employed a 5D anisotropic kernel, constructed from the Hadamard product of 5 1-D kernels $k(\boldsymbol{x}, \boldsymbol{x'}) = \sigma^2 \prod_d k(x_d, x'_d)$, and developed a flexible kernel selection for each dimension using Radial Basis Functions (RBF), linear, Matern, and periodic kernel forms (Eqn. 1). At each iteration, a stimulus was presented, the GP model was updated with the

corresponding neural response, and the updated GP was then used to determine the next optimal stimulus.

$$\begin{cases} k_{RBF}(x_d, x'_d) = \exp(-\frac{(x_d - x'_d)^2}{2\ell_d^2}) \\ k_{\text{linear}}(x_d, x'_d) = x_d x'_d \\ k_{M5/2}(x_d, x'_d) = (1 + \frac{\sqrt{5(x_d - x'_d)^2}}{\ell_d} + \frac{5(x_d - x'_d)^2}{3\ell_d^2}) \exp(-\frac{\sqrt{5(x_d - x'_d)^2}}{\ell_d}) \\ k_p(x_d, x'_d) = \exp(-\frac{2\sin^2(\pi|x_d - x'_d|/p)}{\ell_d^2}) \end{cases}$$

Equation 1: Kernel Formulae

For each neuron, the optimization loop was terminated once the Expected Improvements (EI) $\text{EI} = \bar{\sigma}(\boldsymbol{x})(Z \cdot \Phi(Z) + \phi(Z)), Z = \frac{\bar{f}(\boldsymbol{x}) - f(\boldsymbol{x}_{best})}{\bar{\sigma}(\boldsymbol{x})}$ or EI with corrected posterior uncertainty [9] $\text{EI}^C = \bar{\sigma}^C(\boldsymbol{x})(Z^C \cdot \Phi(Z^C) + \phi(Z^C)), \bar{\sigma}^C(\boldsymbol{x}) = \sqrt{\sigma^2(\boldsymbol{x}) + \sigma^2(\boldsymbol{x}_{best}) - 2\sigma(\boldsymbol{x}, \boldsymbol{x}_{best})}, Z^C = \frac{\bar{f}(\boldsymbol{x}) - f(\boldsymbol{x}_{best})}{\bar{\sigma}^C(\boldsymbol{x})}$ fell below a threshold, at which point the system moved to the next neuron for optimization.

Results and Conclusions: Using this novel system, we collected data from the primary visual cortex of five mice (expressing GCaMP6s, 6f), aggregating a dataset of ~6.5k responsive neurons. To compare with known single-dimensional orientation preference across the population, we analyzed the distribution of tuning peaks and compared neurons preferentially tuned to cardinal versus non-cardinal directions. Results showed an over-representation on the cardinal directions for orientation tuning ($\chi^2 = 52.42$, $p<0.001$), consistent with prior work [10].

To identify functional cell types, we performed K-mean clustering (k=14) on the 5D peak locations of all neurons and observed distinct clusters (Fig. 2). For example, one cluster is tuned to large, low-contrast, ventro-temporal stimuli and another is tuned to medium-sized, high-contrast, dorso-temporal stimuli. While their spatial and contrast preferences were divergent, both subtypes showed similar tuning for medium speeds and higher numerosity.

Our real-time system enabled *in vivo* characterization of high-dimensional neural tuning and revealed distinct functional types within the mouse primary visual cortex. By adaptively guiding stimulus selection, this approach markedly reduced experimental time while uncovering complex tuning interactions that underlie functional organization in the visual cortex.

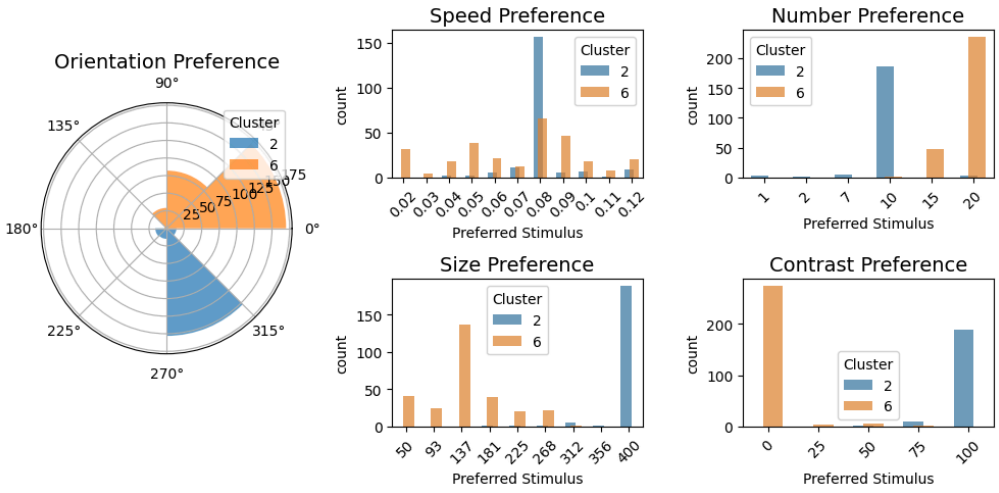

Figure 2: Tuning preferences of functional neuron clusters

Reference:

1. Ogawa T, Komatsu H. Target selection in area V4 during a multidimensional visual search task. Journal of Neuroscience. 2004 Jul 14;24(28):6371-82.
2. Yerxa TE, Kee E, DeWeese MR, Cooper EA. Efficient sensory coding of multidimensional stimuli. PLoS computational biology. 2020 Sep 24;16(9):e1008146.
3. Muzzu T, Saleem AB. Feature selectivity can explain mismatch signals in mouse visual cortex. Cell reports. 2021 Oct 5;37(1).
4. Stringer C, Pachitariu M, Steinmetz N, Carandini M, Harris KD. High-dimensional geometry of population responses in visual cortex. Nature. 2019 Jul 18;571(7765):361-5.
5. Yao M, Wen B, Yang M, Guo J, Jiang H, Feng C, Cao Y, He H, Chang L. High-dimensional topographic organization of visual features in the primate temporal lobe. Nature Communications. 2023 Sep 22;14(1):5931.
6. Draelos A, Loring MD, Nikitchenko M, Sriworarat C, Gupta P, Sprague DY, Pnevmatikakis E, Giovannucci A, Benster T, Deisseroth K, Pearson JM. improv: A software platform for real-time and adaptive neuroscience experiments. bioRxiv. 2021 Feb 23:2021-02.
7. Giovannucci A, Friedrich J, Gunn P, Kalfon J, Brown BL, Koay SA, Taxidis J, Najafi F, Gauthier JL, Zhou P, Khakh BS. CaImAn an open source tool for scalable calcium imaging data analysis. elife. 2019 Jan 17;8:e38173.
8. Zhou H, Ma X, Blaschko MB. A corrected expected improvement acquisition function under noisy observations. InAsian Conference on Machine Learning 2024 Feb 27 (pp. 1747-1762). PMLR.
9. Jimenez LO, Tring E, Trachtenberg JT, Ringach DL. Local tuning biases in mouse primary visual cortex. Journal of Neurophysiology. 2018 Jul 1;120(1):274-80.