Dendritic Ca2+ as a Predictor of Stimulus Perception and Behavior

Uni- and Multivariate Analysis

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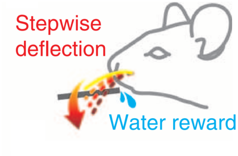
September 13, 2017

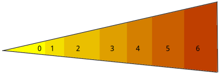
BCCN Berlin

Introduction

The Experiment

Takahashi et al. 2016





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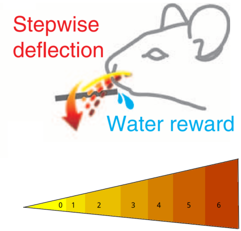
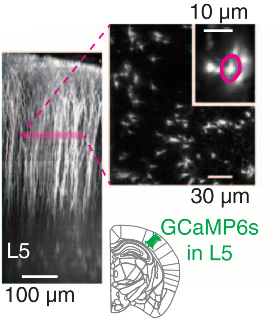
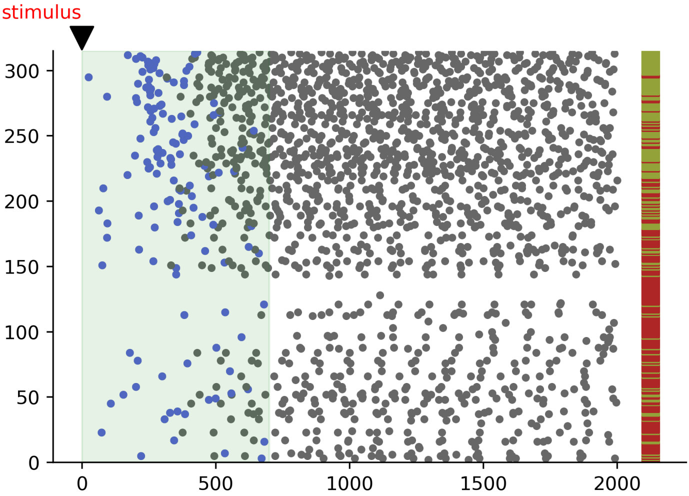
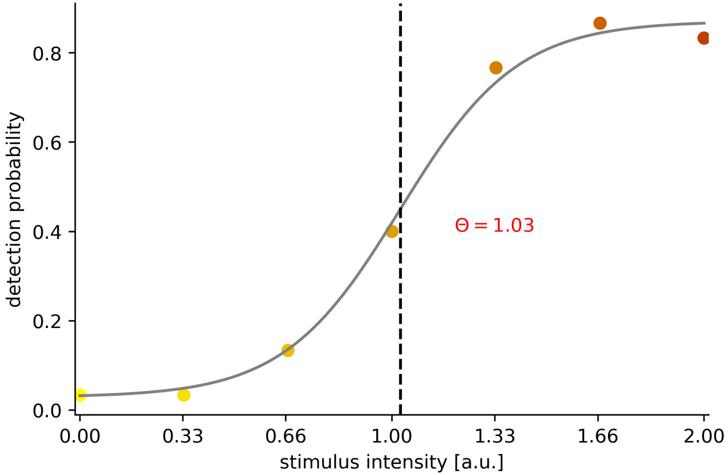




The Data - Behavioral

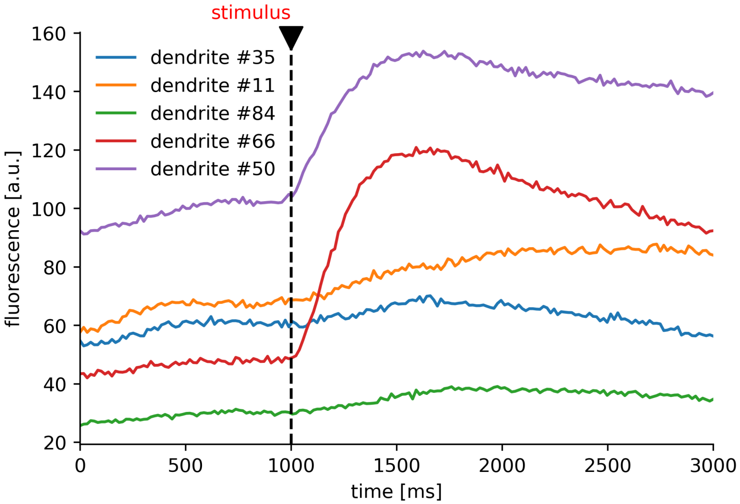


The Data - Psychometric Curve



The Data - Neuronal

Trial-averaged Ca^{2+} fluorescence traces of random dendrites



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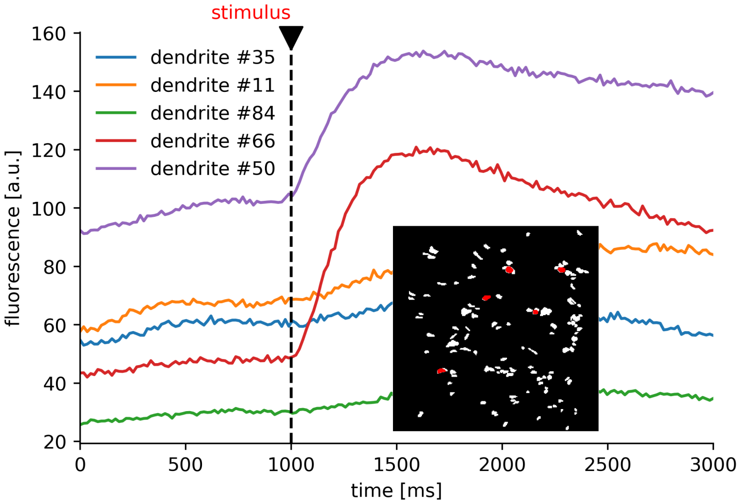

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- What is the relationship between Ca2+ activity and stimulus intensity/behavior
- Can we build predictive classifiers for this data?
- Does a multivariate approach give us any significant advantage over a univariate one?

Univariate Analysis

SVM - What is an SVM?

Figure - xkcd

SMV...

- is a supervised learning algorithm
  - uses labelled data
- has a regularization parameter that can combat overfitting
- is good for small samples with many features (in theory)

SVM - What is an SVM?

Works on linearily separable and nonseparable data of **arbitrary dimension**

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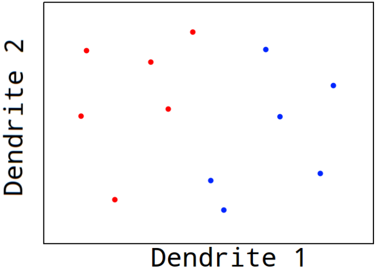

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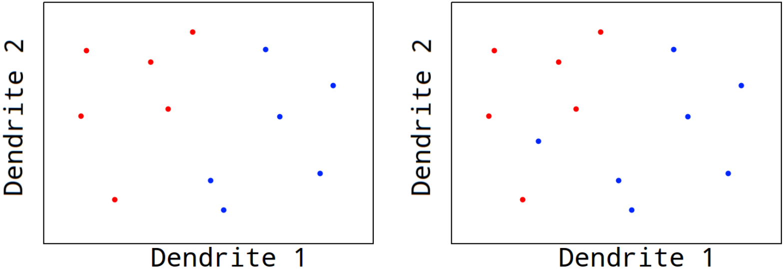
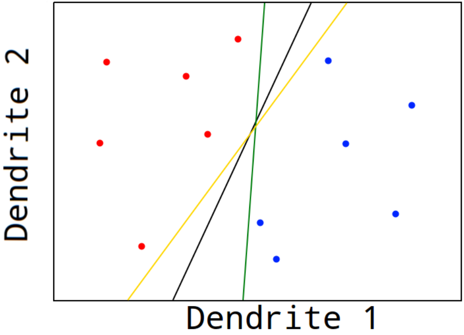


SVM - What is an SVM? Linearily Separable Case

There are many separating hyperplanes, but which one is best?



SVM - What is an SVM? The Margin

The one that maximizes the hyperplanes' distance from the nearest datapoints of either class while classifying all data correctly - **the margin**

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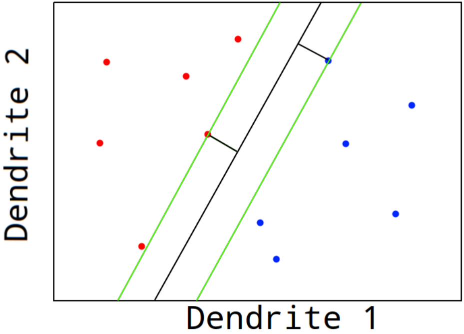

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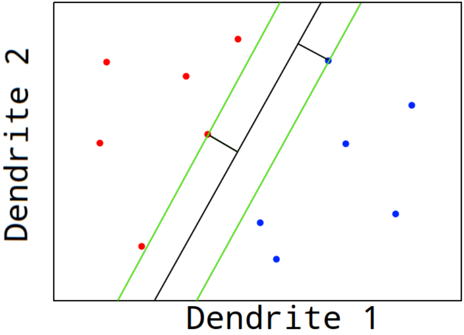
The hyperplane is given by

$$g(\mathbf{x}) = \mathbf{w}^{\mathsf{T}}\mathbf{x} + \mathbf{b}$$



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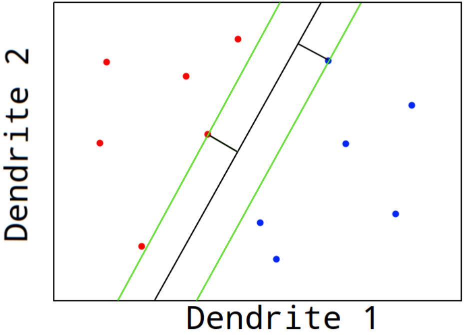
It turns out that the margin is given by $\frac{2}{||w||}$ and we maximize it by minimizing

$$\frac{1}{2}||\mathbf{w}||_2^2$$



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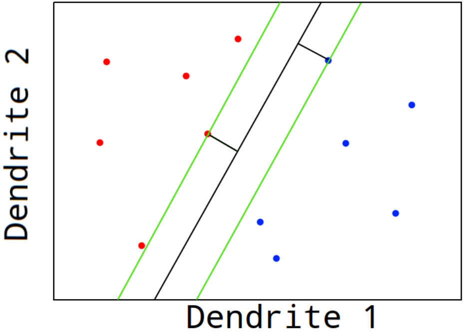
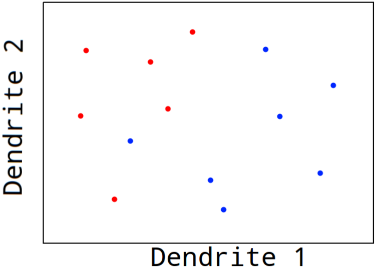
under the constraint that **all data are classified correctly**.



SVM - What is an SVM? Linearily Nonseparable/Noisy Data



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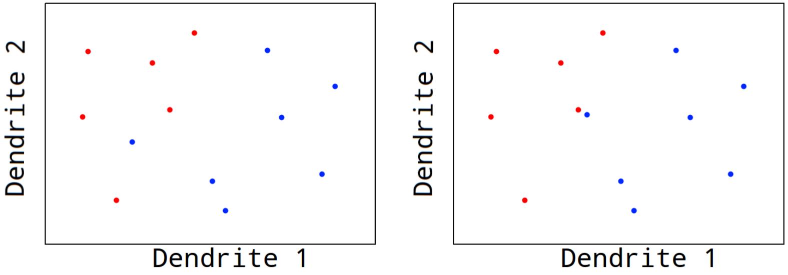

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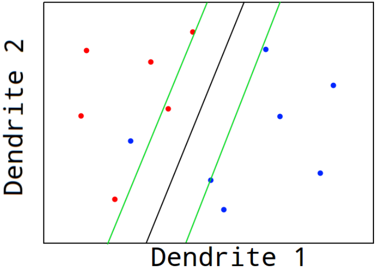

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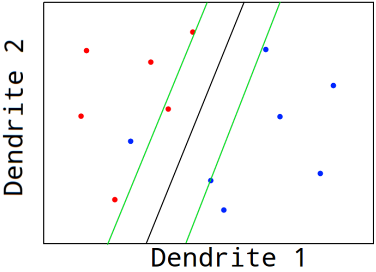

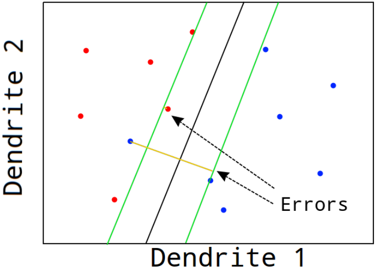

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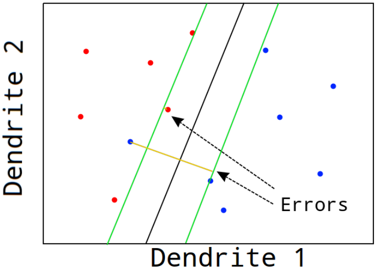
Instead of $\frac{1}{2}||\mathbf{w}||_2^2$ we now minimize

$$\frac{1}{2}||\mathbf{w}||_2^2 + C\sum_{i=1}^{n}\xi_i$$



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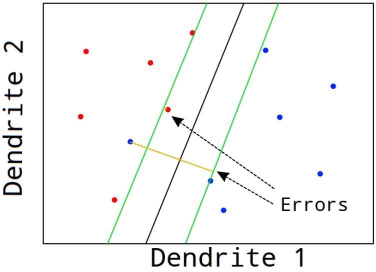

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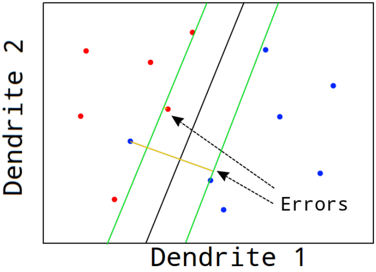
The parameter C lets us now control the tradeoff between the generalization and training error (overfitting).



SVM Specifics

- All data are normalized to zero mean and unit variance

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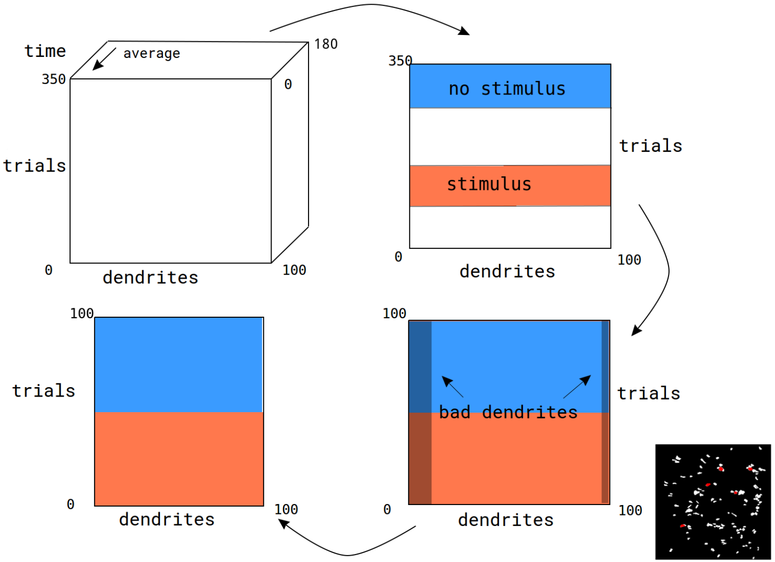
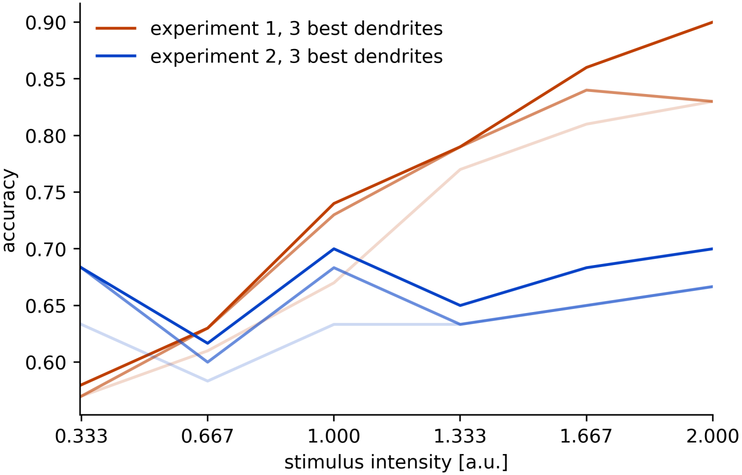
- Crossvalidation is performed to conrol for overfitting

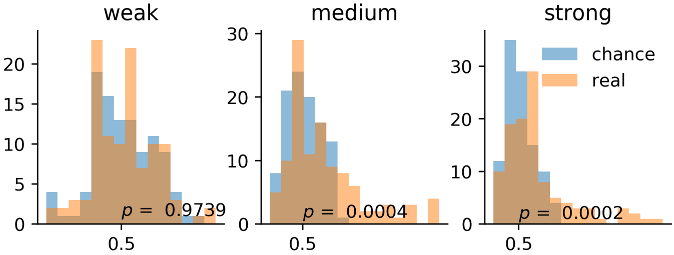
Stimulus Presence Detection



SVM - Most Accurate Dendrites



SVM - Statistical Significance



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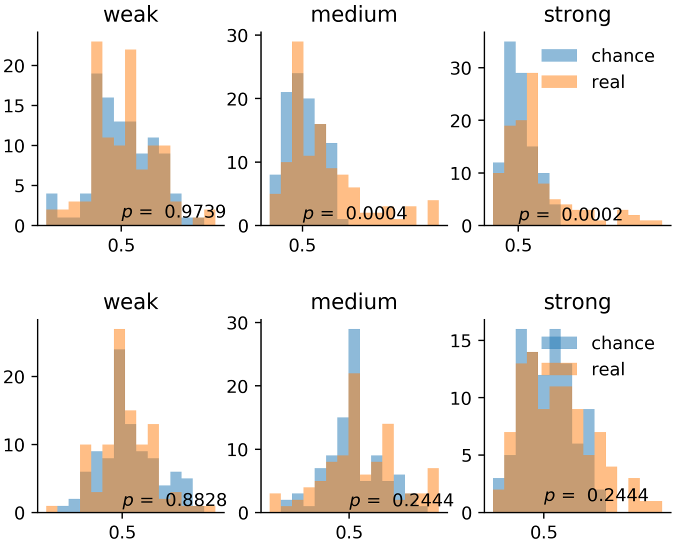

Rank Order Correlation

We want to quantify the similarity between two rank orders of dendrites R and Q, which both have length n. For example, we would like to see whether similar dendrites react to similar stimuli.

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Dendrite	R_i	Q_i	R_{acc}	Q_{acc}
1	1	2	0.78	0.81
2	2	1	0.72	0.76
3	3	3	0.65	0.70
4	4	4	0.58	0.57
5	5	16	0.51	0.53
6	6	75	0.53	0.48
7	7	8	0.51	0.52
8	8	89	0.52	0.49
9	9	100	0.50	0.51
...	...	...	...	...

Rank Order Correlation

Standard approach: **Spearman's rank order coefficient** ρ

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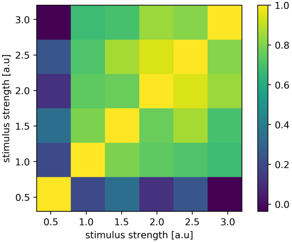
We use a modified version of that because we usually have **many uninformative dendrites** that can skew the result (their exact rank is unimportant).

Rank Order Correlations of Dendrites Over Stimuli

Experiment 1



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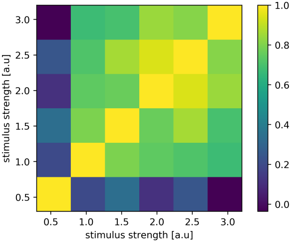
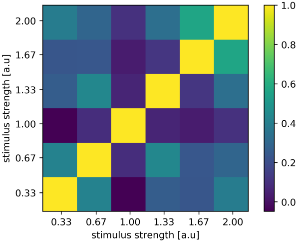


Experiment 2



Responses of One Dendrite to Different Stimuli

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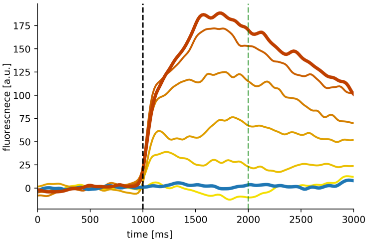

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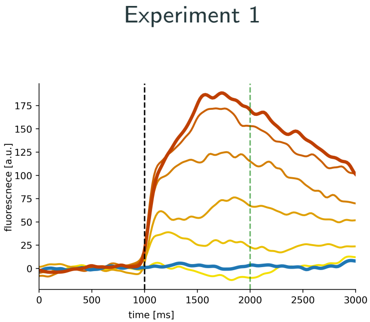
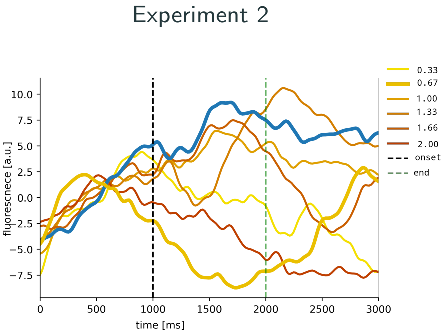
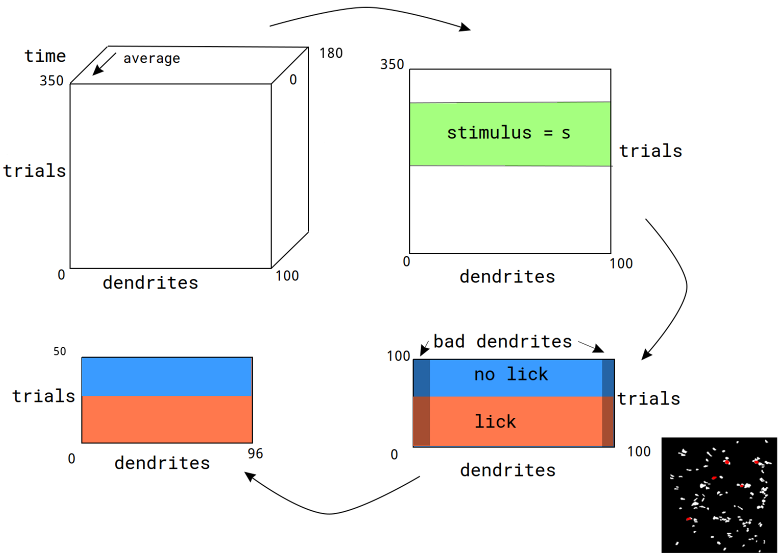




Behavior Detection

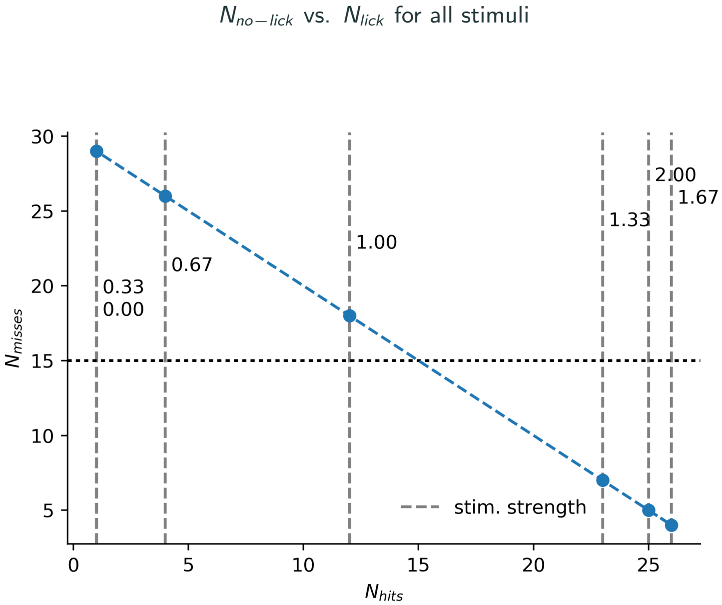


Behavioral Prediction - Most Accurate Dendrites

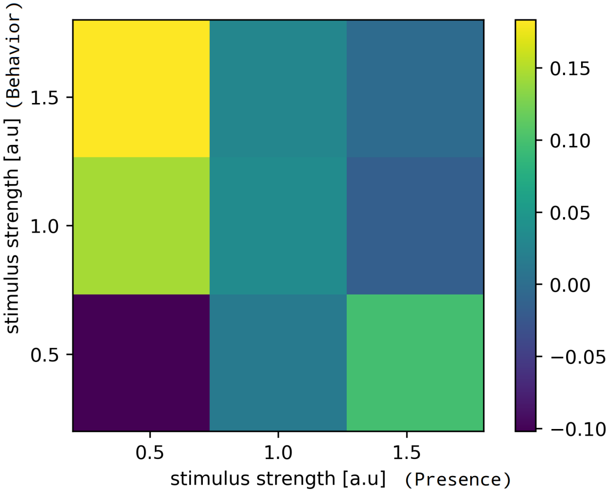
Different dataset - Stimulus strength 1 (near threshold)

Dendrite #	μ_{acc}	σ_{acc}
88	0.80	0.08
57	0.80	0.08
92	0.78	0.06
56	0.76	0.10

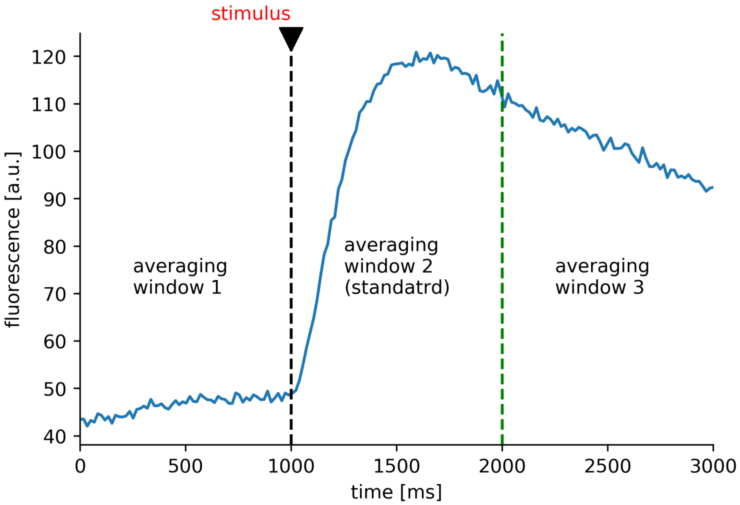
Behavioral Predition - Imbalance



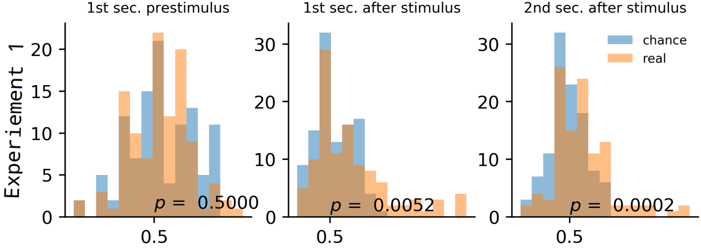
Rank Order Correlations of Best Behavior and Presence Dendrites



Timing - What if We Use Different Averaging Windows?



Timing - Statistical Significance



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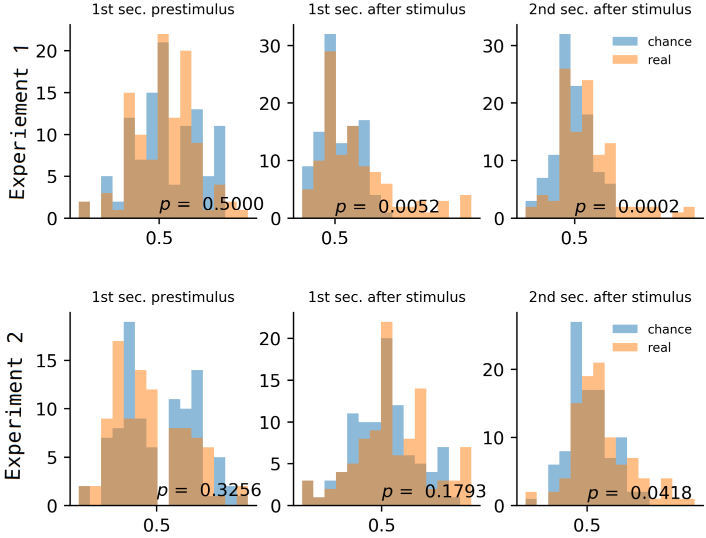
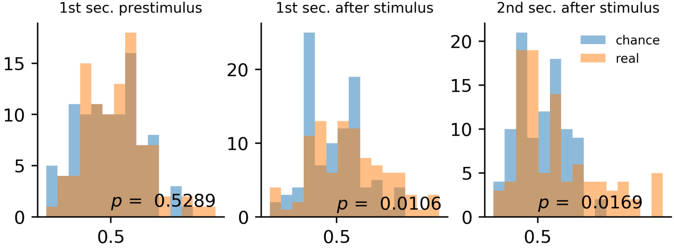


Statistical Significance - Behavior

At threshold stimulus ≈ 1



Multivariate SVM Analysis

Presence Detection - Feature Selection

Since we have fewer datapoints per condition (30-50 per class) than features (100-150), we are prone to overfit to noise (which is abundant in our data).

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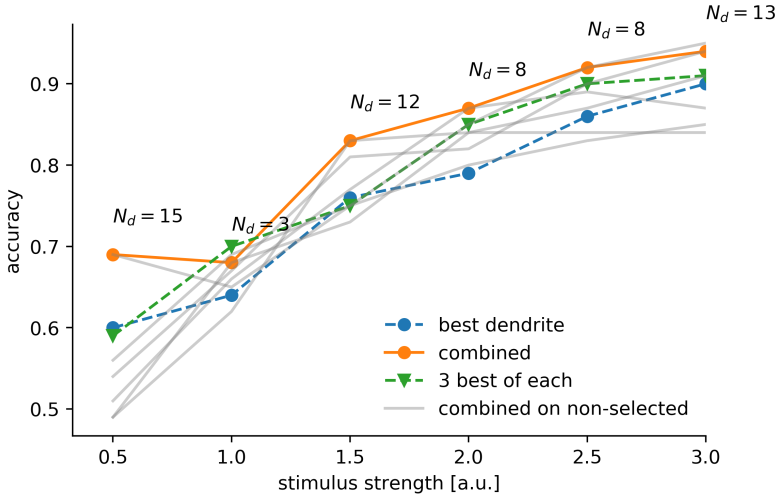
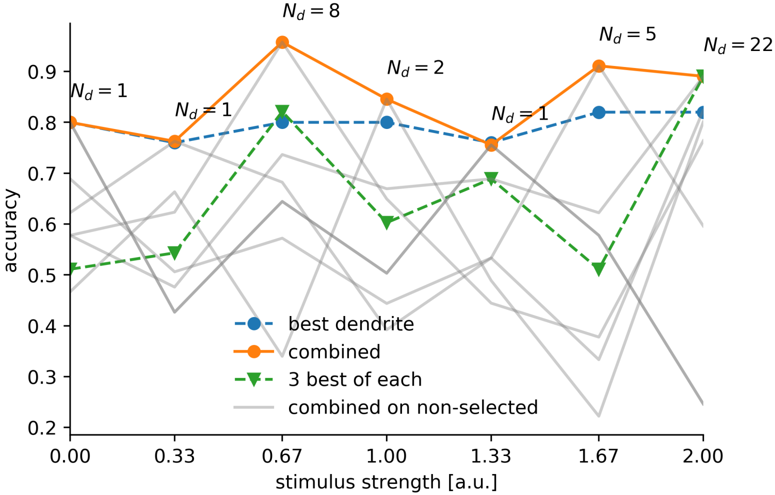
$\Rightarrow$ we have to do **feature selection**.

We can use the previously best discriminating dendrites.

SVM Performance on Combined Dendrites - Presence Detection, Experiment 1



SVM Performance on Combined Dendrites - Behavioral



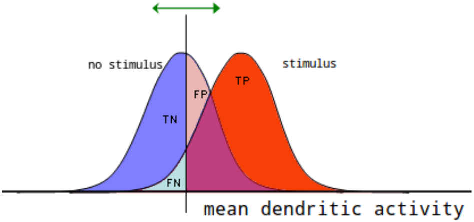
Conclusions

- We can build high accuracy classifiers based on this data
- Multivariate analysis is advantageous
- Prestimulus Ca2+ activity does not predict the animal's decision
- Different dendrites code for stimulus and behavior
- There are very large differences between different animals/experiments
- We need more data - particularily for multivariate analysis

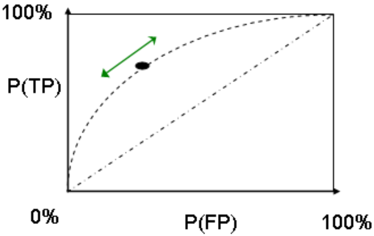
- Takahashi, N., Oertner, G. T., Hegemann, P. & Larkum, E. M. Active cortical dendrites modulate perception. Science 335, 1587-1590 (2016)
- Mante V., Sussillo D., Shenoy KV., Newsome WT. Context-dependent computation by recurrent dynamics in prefrontal cortex. Nature 503, 78-84 (2013)
- Pinto da Costa, J. New Results in Weighted Correlation and Weighted Principal Component Analysis with Applications, Chapter 2 (2015)

Extra Slides

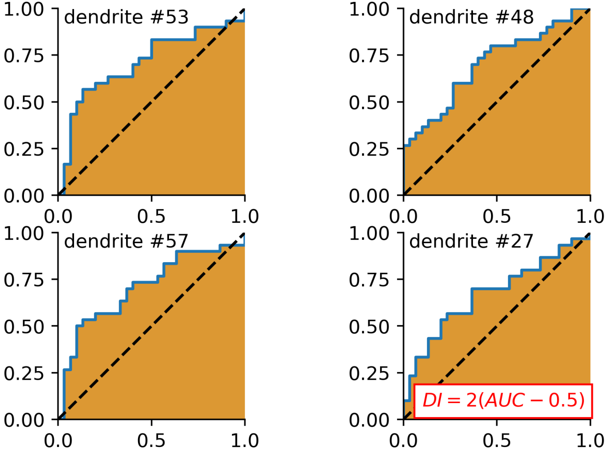
ROC



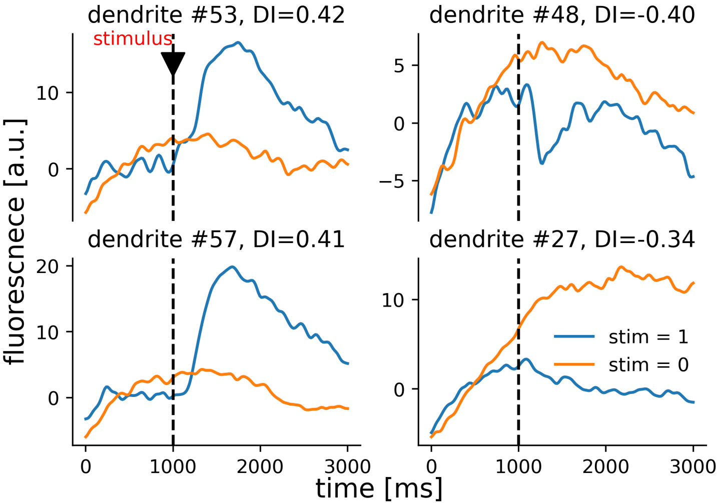
TP	FP
FN	TN
1	1



ROC - Best ROC Curves

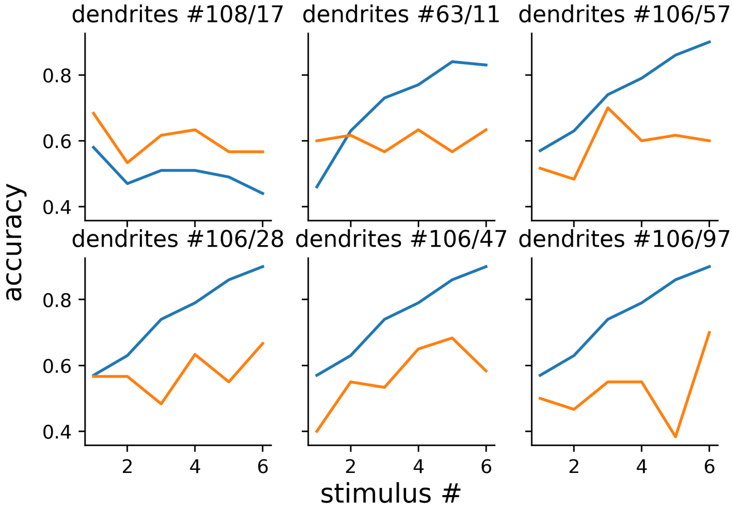


Ca^{2+}-Traces of Largest $|\mathbf{AUC} - 0.5|$-Dendrites

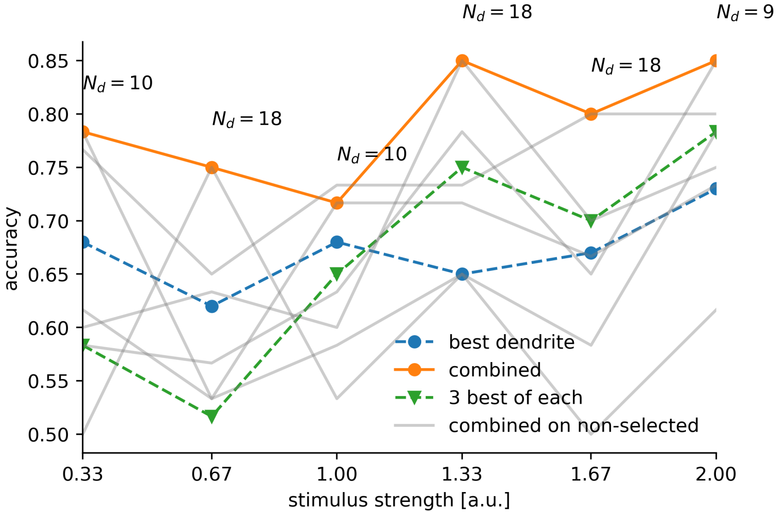


Near threshold-stimulus (≈ 1)

Tuning Curves



SVM Performance on Combined Dendrites - Presence Detection, Experiment 2



Weighted Rank Order Correlation Coefficient

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Standard approach: Spearman's rank order coefficient

$$\rho(R, Q) = 1 - \frac{6 \sum_i^n D_i^2}{n(n^2 - 1)}$$

where $D_i = R_i - Q_i$.

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Problem: Many of the dendrites are not significant for classification but affect ρ greatly. We would like to be able to **weight our $\mathbf{D_i}$**'s.

Weighted Rank Order Correlation Coefficient

We want our rank order coefficient to be an affine linear function of $\sum_i w_i D_i^2$:

$$\rho_W(R, Q) = A + B \sum_i^n w_i D_i^2$$

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Thus:

$$\boxed{\rho_W(R, Q) = 1 - \frac{-2 \sum_i^n w_i D_i^2}{\sum_i^n w_i (n - 2i + 1)^2}}$$

Weighted Rank Order Correlation Coefficient

One possible solution:

$$\rho_W(R, Q) = 1 - \frac{-2\sum_i^n w_i D_i^2}{\sum_i^n w_i (n - 2i + 1)^2}$$

With a monotonicity constraint on W.

Population Response in Task Variable Space

We would like to visualize the time evolution of the population response in a coordinate system in which the axes represent stimulus strength and choice.

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To that end we use linear regression to write the normaized response of dendrite i at time t in trial k as a linear combination of these task variables:

$$r_k^{i,t} = \beta_1^{i,t} choice_k + \beta_2^{i,t} stimulus_k + \beta_3^{i,t}$$

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The regression coefficients $\beta_\nu^{i,t}$ describe how much the activity of dendrite i at time t in trial k corresponds with variable ν.

Population Response in Task Variable Space

We define

$$\mathbf{F} = \begin{bmatrix} \mathit{choice}_1 & ... & \mathit{choice}_n \\ \mathit{stimulus}_1 & ... & \mathit{stimulus}_n \\ 1 & ... & 1 \end{bmatrix}$$

and estimate for each dendrite i and timepoint t

$$\beta^{\boldsymbol{i,t}} = (\mathbf{F}\mathbf{F}^{\mathbf{T}})^{-\mathbf{1}}\mathbf{F}\mathbf{r}^{\mathbf{i,t}}$$

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The goal is to use β to find a two-dimensional subspace of the dendrite space into which we can transform $\mathbf{x^{c,t}}$.

Population Response in Task Variable Space

We then use PCA to denoise the data matrix

$$\mathbf{X} = \begin{bmatrix} \mathbf{x}_{\mathbf{c_1},\mathbf{t_1}} & \dots & \mathbf{x}_{\mathbf{c_1},\mathbf{t_n}} & \dots & \mathbf{x}_{\mathbf{c_m},\mathbf{t_n}} \end{bmatrix}$$

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and we apply the denoising matrix to all $\beta^{\boldsymbol{\nu},\boldsymbol{t}}$ as well, which yields the denoised regression vectors

$$\beta^{\boldsymbol{\nu},\boldsymbol{t}}_{\boldsymbol{pca}}$$

Since the $\beta_{\boldsymbol{pca}}^{\boldsymbol{\nu},\boldsymbol{t}}$ are time variing but we would like a coordinate system that is fixed in time, we "freeze" them at the point in time at which there is maximum correlation:

Population Response in Task Variable Space

Since the $\beta^{\nu,t}_{pca}$ are time variing but we would like a coordinate system that is fixed in time, we "freeze" them at the point in time at which there is maximum correlation:

$$\beta^{\nu}_{max} = \beta^{\nu,t^{\nu}_{max}}_{pca}$$

$$t^{\nu}_{max} = argmax_t ||\beta^{\nu,t}_{pca}||$$

Population Response in Task Variable Space

We would like these β^{ν}_{max} to be the basis vectors of our new coordinate system, however, they are not yet orthogonal.

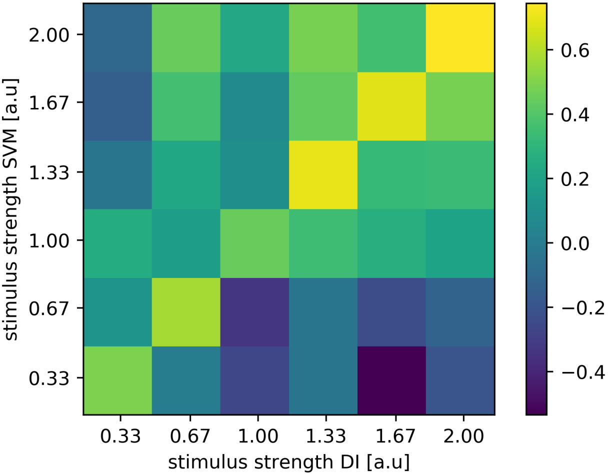
Population Response in Task Variable Space

We would like these $\boldsymbol{\beta}^{\boldsymbol{\nu}}_{\boldsymbol{max}}$ to be the basis vectors of our new coordinate system, however, they are not yet orthogonal. We fix this by applying QR-decomposition to

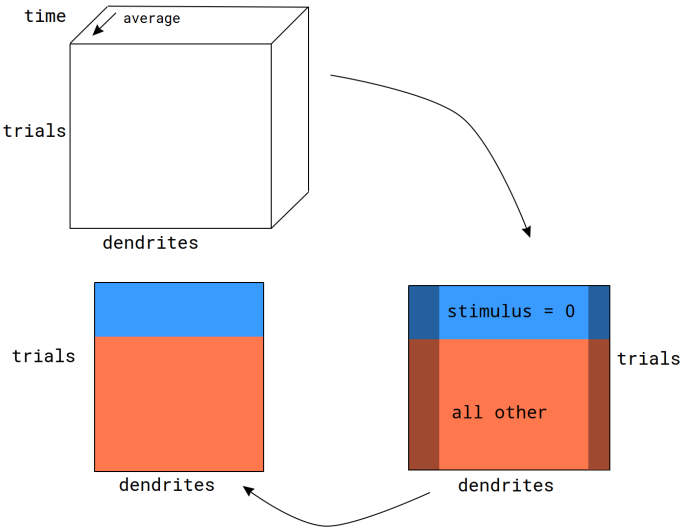
$$\mathbf{B}^{\mathbf{max}} = \begin{bmatrix} \beta^{\mathbf{1}}_{\mathbf{max}} & \beta^{\mathbf{2}}_{\mathbf{max}} \end{bmatrix} = \mathbf{QR}$$

where $\mathbf{Q}$ is an orthogonal matrix whose columns $\boldsymbol{\beta}^{\boldsymbol{\nu}}_{\perp}$ are the **basis vectors** of our new coordinate system. We can now transform our data into it.

DI and SVM Dendrite Rank Order Correlation



SVM Performance on Combined Dendrites - Global Presence



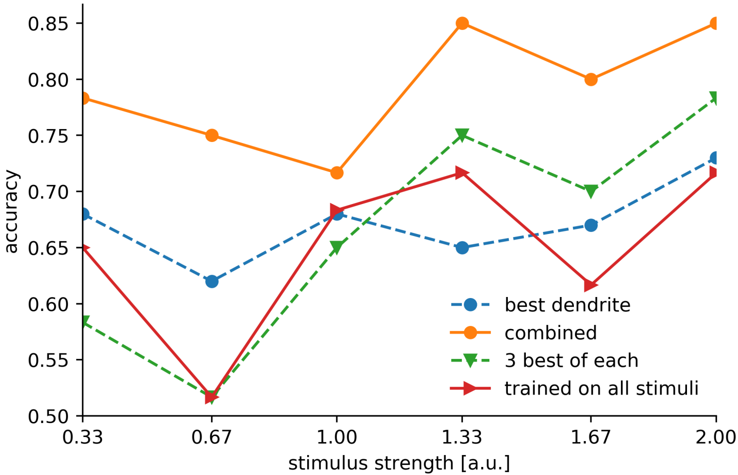
SVM Performance on Combined Dendrites - Global Presence

Performance on global presence detection:

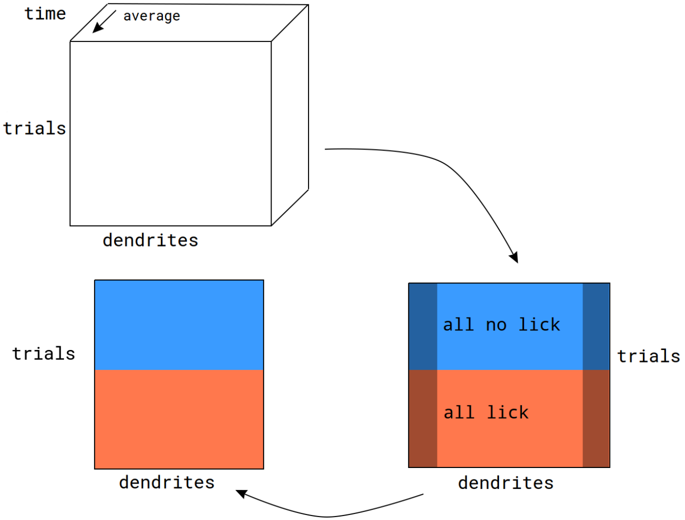
Mean: 0.68

Standard deviation: 0.08

SVM Performance on Combined Dendrites - Presence Detection



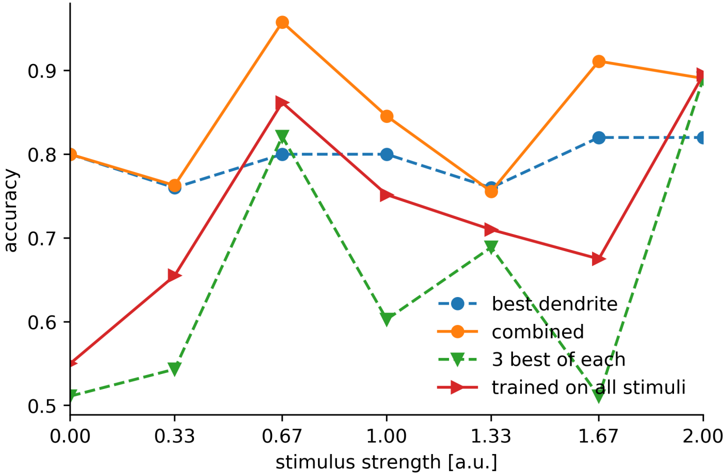
SVM Performance on Combined Dendrites - Global Behavior



SVM Performance on Combined Dendrites - Global Behavior

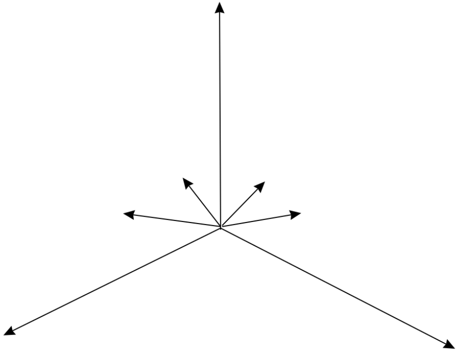
Performance on global presence detection:
Mean: 0.71
Standard deviation: 0.1

SVM Performance on Combined Dendrites - Behavioral



Population Coding

Population Coding - Idea (Mante, Sussillo 2013)



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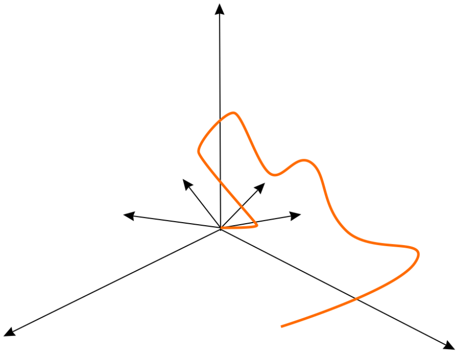

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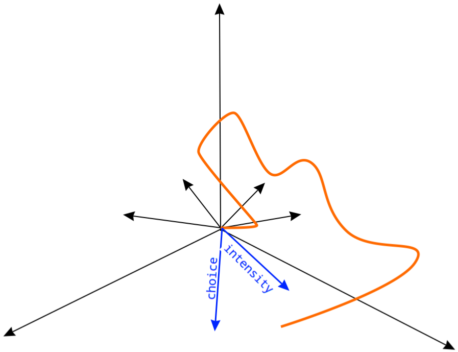

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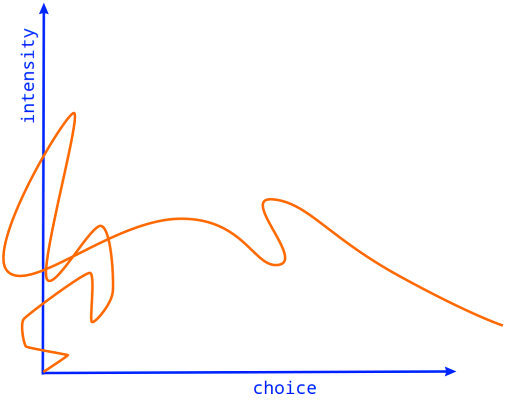
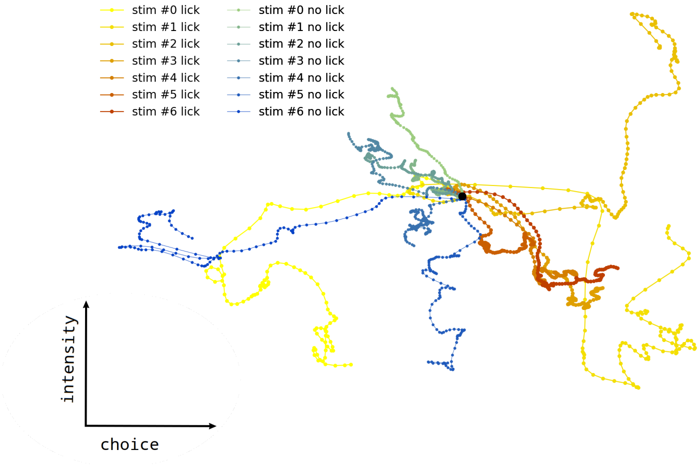


Population Response in Task Variable Space

Solve Problem with combined SVM first



Population Response in Task Variable Space

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