Making sense of high-dimensional neural activity during complex behavior

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11/18/2017
What happens in the brains of animals as they interact with conspecifics?

Expression of social behaviors depends on an animal’s age, sex, social status, past experiences, and level of stress.
Marr’s three levels of analysis applied to social behavior

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**Top-down**

*Computational*  
- What does the animal need to do to survive and reproduce?

*Algorithmic*  
- What control strategy does it use to determine its actions?

*Implementation*  
- How is this control strategy manifested in the brain?

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von Frisch, Lorenz, and Tinbergen shared the 1973 Nobel Prize in Medicine for their work on organization and elicitation of individual and social behavior patterns.
Marr’s three levels of analysis applied to social behavior

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**Implementation**
- How is this control strategy manifested in the brain?

Bottom-up

Identify brain areas involved in behavior

Determine connectivity between them

Observe their activity during these behaviors
Where to look?

Reproductive

- MPO
- VMHvl
- PMv

Defensive

- AHN
- VMHdm
- PMd

optogenetic stimulation

Photostimulation intensity

<table>
<thead>
<tr>
<th>Weak</th>
<th>Moderate</th>
<th>Strong</th>
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<tbody>
<tr>
<td>Mounting</td>
<td>Mixed</td>
<td>Attack</td>
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Pheromonal cues

- VNO
- AOB
- MeA PD
- BNST PR
- VMHvl
- periaqueductal gray
- spinal cord

Lee et al, 2014
We can visualize the electrical activity of neurons using GCaMP.

The concentration of calcium in neurons transiently increases when they spike.

Drive production of GCaMP in a genetically defined target population of cells in the brain.

Calcium imaging of neuron activity in the mouse brain.
Microendoscopes let us look at GCaMP fluorescence in a freely behaving animal.
Microendoscopes let us look at GCaMP fluorescence in a freely behaving animal

50 - 300 simultaneously imaged neurons (out of ~2000 in VMHvl)

x 14 trials/day (5 male, 5 female, 2 toy, 2 baseline) x 3 days

Manual, frame-by-frame annotation
Four approaches to making sense of imaging data
1. Dimensionality reduction tells us about the largest sources of variance in the data

This can be informative, if you’re lucky.

If you’re not lucky, you can try a semi-supervised method:

“Find me the largest source of variance that is correlated with variable X”:
- Partial least squares regression
- Difference of covariances

“Find me the largest source of variance that has the specified dynamics (e.g., smoothness, rotations)”
- Gaussian process factor analysis (GPFA)
- jPCA
2. Analysis of neural tuning tells us what individual cells respond to
Units can encode more than one thing

**Model A**
- Male cues → Behavior outputs
- Female cues → Behavior outputs

**Model B**
- Male cues → Behavior outputs
- Female cues → Behavior outputs

### Consumption Behaviors
- Mount
- Attack
- Sniff Φ
- Sniff Φ

### Appetitive Behaviors
- Mount-tuned
- Mount-and-attack-tuned
- Attack-tuned
- Attack-and-sniff Φ-tuned
- Sniff Φ-tuned
- Sniff Φ-and-sniff Φ-tuned
- Sniff Φ-tuned
3. Decoders/classifiers tell us what information can be read out from the network.

Train linear classifier to predict behavior from imaged activity of neurons:
- SVM
- Naïve Bayes
- Perceptron
- Fisher's linear discriminant

Linear classifiers are a lot like neurons, in principle.
We can try to decode current behavior from the activity of neurons:
We can use decoding to ask when information appears in the system:

How long does the animal take to determine the sex of the intruder mouse?
We can investigate the appearance and disappearance of predictable states in the network:

- Predict future behavior from current neural activity ("preparatory activity")
- Predict past inputs from current neural activity ("memory trace")
4. Measures of distance tell us how similar two neural states are

**Pearson’s correlation**

- Compute time-averaged response of each neuron to males and to females
- Measure the angle between the vectors to the centers of the two distributions

**Mahalanobis distance**

- Hold out one mouse for testing
- Find distribution of data from remaining♂/♀ mice in neural activity space
- Compute distance of held-out mouse from both distributions, in units of standard deviations in each dimension.
- Take the difference between (the log of) these distances.
Measuring distance can overcome floor/ceiling effects encountered by decoders
A surprise: tracking male/female separation across trials revealed a change in representations:

x 14 trials/day (5 male, 5 female, 2 toy, 2 baseline) x 3 days

Pearson’s corr. with same-day avg representations
Encounter number is a poor predictor for separation... but behavior, specifically mounting + anogenital sniffing, is a good predictor!
Follow-up experiments

Free access to intruders is required for separate representations to form.

Mice that don’t show separation don’t attack.
Hypothesized narrative

1. Sexual experience
2. Reward signal?
3. Increased aggression

Pheromonal cues

VNO → AOB → MeA

BNST

VMH

Increased aggression

Periaqueductal gray

Spinal cord

Cell responses

Male Female
Future directions

• Improve our description of the behaviors in question

Video posted at
https://www.youtube.com/watch?v=YZgzv4td7Yw

+ Cristina Segalin, Jalani Williams, Pietro Perona
Future directions

- Improve our description of the behaviors in question
- **Build models of the control of social behavior by multiple brain areas**
- Compare VMHvl data to activity of other social behavior areas
- Look at other context changes that affect behavioral strategy
David Anderson lab
neural circuits for innate emotional behaviors

Mouse group
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Prabhat Kunwar
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Thank you!