

Causal models of brain dynamics

Unsupervised learning of optogenetic experiments via deep
generative models

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Deisseroth and Druckmann Labs



Qualifying Exam
Neurosciences PhD Program
Stanford University

June 17, 2019

2019-06-13





2019-06-13

Motivation

Aim 1: What is the most effective approach to model whole-brain data?

Aim 2: How do we address the problem of underdetermination?

Aim 3: Do the model substructures map to underlying biology?

Roadmap

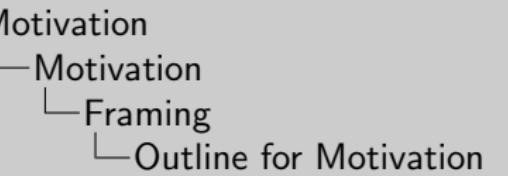
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1. I will first talk about why my overall goal is predicting neural activity, and discuss the importance of causal models as opposed to merely descriptive ones. I will further motivate this modeling goal by describing applications that are enabled by this approach.
2. In my first aim, I propose that a reasonable direction is to eschew biological plausibility and leverage state-of-art deep learning networks for predicting neural activity, and show that this approach outperforms current brain-wide modeling.
3. For my second aim, I propose a model-based approach to choosing optogenetic stimulation patterns such that we efficiently learn the best model parameters.
4. Finally, in my third aim, I suggest methods to incorporate biological priors as well as explicitly extract biological hypotheses.

Outline for Motivation



2019-06-13



Motivation
Framing
Applications

Aim 1: What is the most effective approach to model whole-brain data?

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Motivation

Framing

Applications

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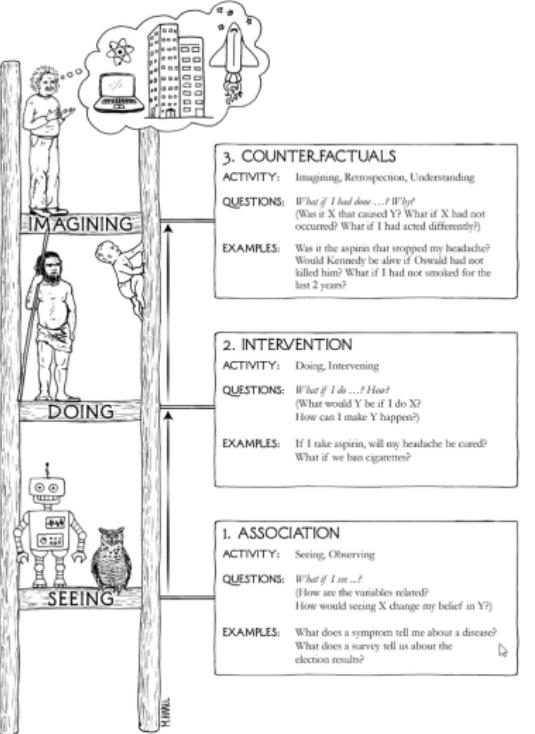
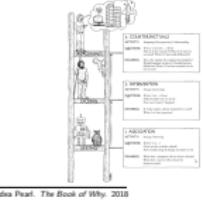
Aim 3: Do the model substructures map to underlying biology?

Climbing the ladder of causation



2019-06-13

Motivation
└ Motivation
└ Framing
└ Climbing the ladder of causation



Judea Pearl. *The Book of Why*. 2018

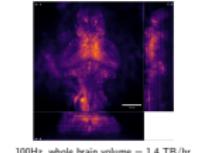
Tyler Benster, Qualifying Exam

Challenge: massive datasets and underlying complexity

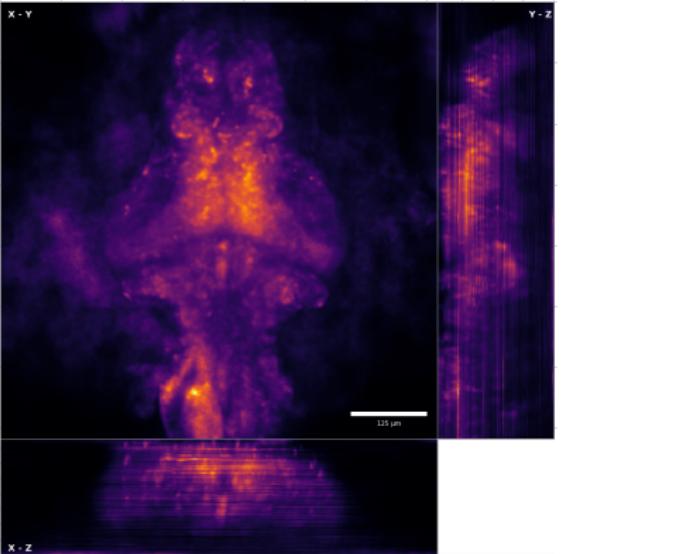


Motivation
└ Motivation
└ Framing
└ Challenge: massive datasets and underlying complexity

2019-06-13



Noah Young, unpublished, 2019



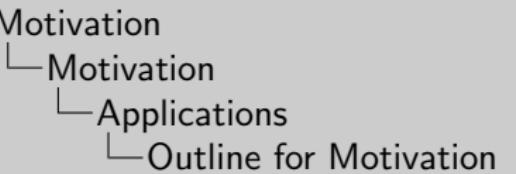
100Hz, whole brain volume = 1.4 TB/hr

Noah Young, *unpublished*, 2019

Outline for Motivation



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Framing

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Motivation
└ Motivation
 └ Applications
 └ Psychiatry



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Let's draw an analogy for healthy vs diseased dynamics: safe vs dangerous driver.

1. static vs temporal: in defensive driving, want to keep staggered position. In static view, minivan driver is dangerous but in temporal view may be healthy as is simply passing the subaru.
2. unit vs population: consider the black sedan following the minivan. If it maintains a consistent following distance by accelerating and braking, then a safe driver, but in a vaccuum with no information of other cars, looks completely erratic.

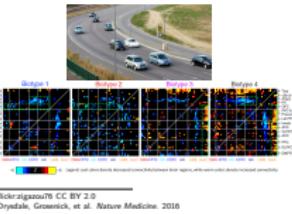
Psychiatry

Model-based summaries of health vs disease



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Motivation
└ Motivation
 └ Applications
 └ Psychiatry



Four functional connectivity "biotypes" from fMRI study of depressed patients. Has no notion of time (one true underlying phenotype capturing different snapshots?), and is not a causal model—where should we stim to nudge dynamics back towards health?

Applications:

- muck with gene, a lot changes → create summary
- “outlierness” of brain dynamics
- model gives reduction of whole data

flickr:zigazou76 CC BY 2.0

Drysdale, Gosenick, et al. *Nature Medicine*. 2016



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Motivation
└ Motivation
 └ Applications
 └ Brain-computer interfaces



<https://youtu.be/9oka8hqsOzg>



Today's BCI often look like moving a cursor around a screen.

<https://youtu.be/9oka8hqsOzg>



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Motivation
└ Motivation
 └ Applications
 └ Brain-computer interfaces



<https://youtu.be/9oka8hqsOzg>
The Matrix 1999.

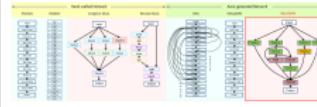


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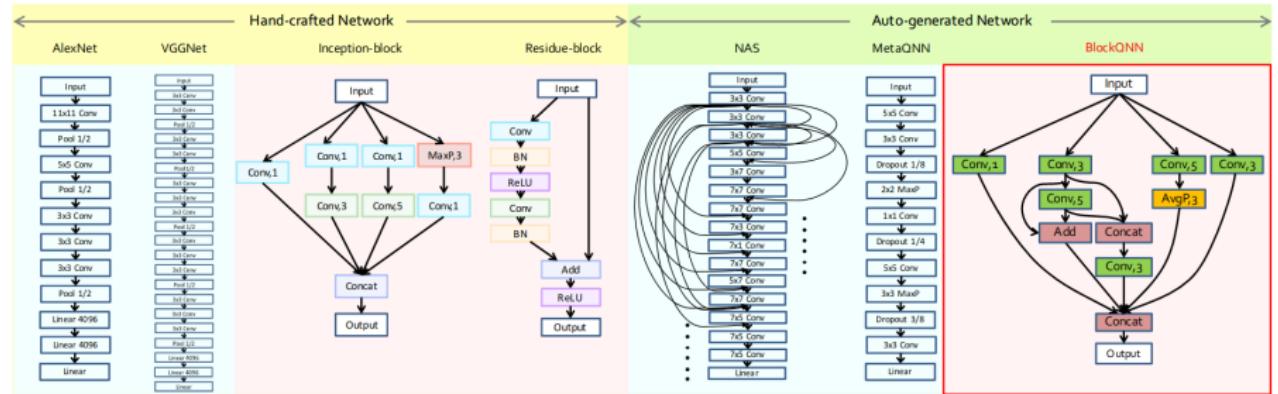


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Motivation
└ Motivation
└ Applications
└ Artificial intelligence



Zhong, et al. CVPR'18



Outline for Aim 1: What is the most effective approach to model whole-brain data?



Motivation

Aim 1: What is the most effective approach to model whole-brain data?

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Aim 1: What is the most effective approach to model whole-brain data?
└ Aim 1: What is the most effective approach to model whole-brain data?
 └ Outline for Aim 1: What is the most effective approach to model whole-brain data?

Motivation
Aim 1: What is the most effective approach to model whole-brain data?
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Hypothesis: deep learning spatial models will outperform traditional point process models



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- Aim 1: What is the most effective approach to model whole-brain data?
 - └ Aim 1: What is the most effective approach to model whole-brain data?
 - └ Hypothesis: deep learning spatial models will outperform traditional point process models

1. First, I will follow a standard preprocessing pipeline to extract the fluorescent traces of individual neurons, and build a recurrent neural network model of the data with one-to-one correspondence between artificial and biological neurons.
2. I will use the raw fluorescence observations of the entire volume to train a deep learning model.
3. Finally, I will compare the performance of both modeling approaches in terms of predicting future observations from withheld test data

The main buy-in for this talk is that having an accurate model of brain dynamics is useful. Most approaches today for brain-wide modeling use hand-crafted features in a preprocessing pipeline that throws away spatial information. How much better can we do at predicting activity if we do not constrain our modeling by biological plausibility?

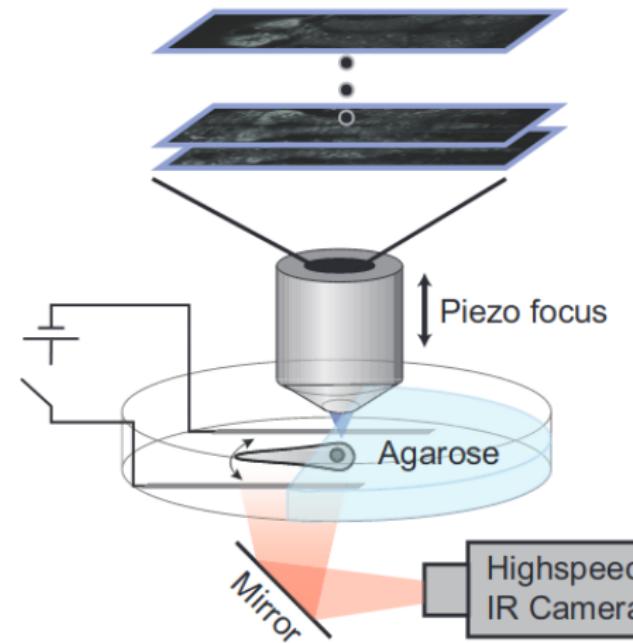
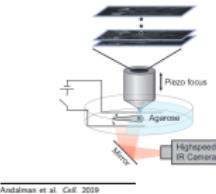
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2P Experimental setup



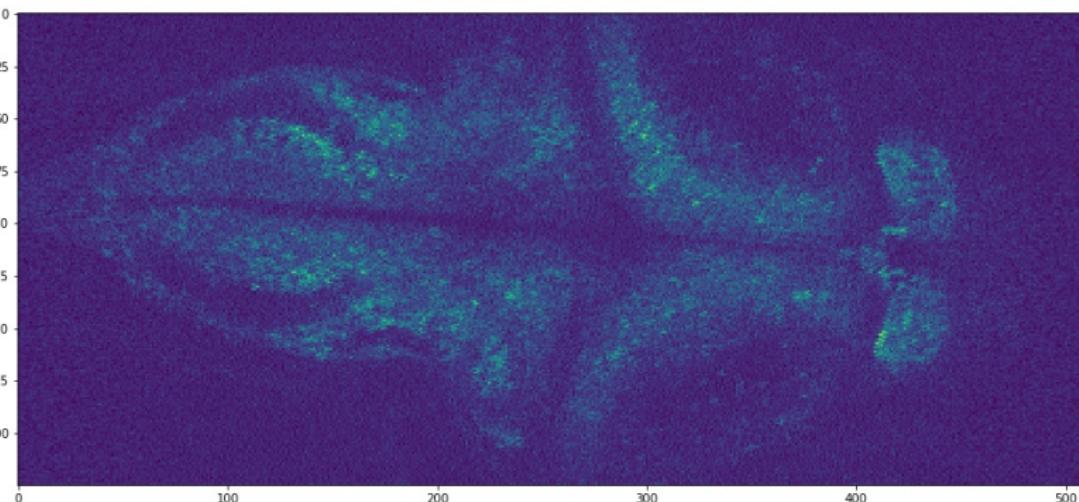
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Aim 1: What is the most effective approach to model whole-brain data?
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 └ 2P Experimental setup



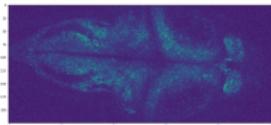
Whole-brain 2P calcium imaging

Z-projection of 19 planes, 4x real-time, 2Hz



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- Aim 1: What is the most effective approach to model whole-brain data?
 - └ Aim 1: What is the most effective approach to model whole-brain data?
 - └ Whole-brain 2P calcium imaging



need to change 2P offset for bidirectional imaging: 2px jitter line-to-line
This is a video. About 2/3 way through, brain goes completely dark (!!), then whole brain lights up.

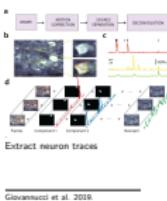
Current approaches to brain-wide modeling



Aim 1: What is the most effective approach to model whole-brain data?

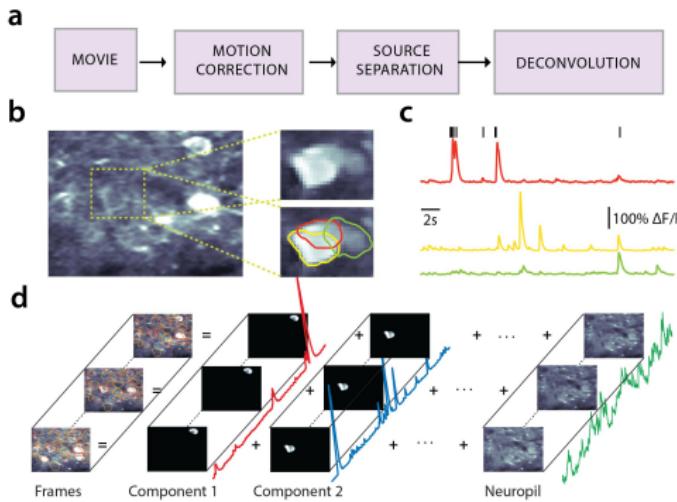
└ Aim 1: What is the most effective approach to model whole-brain data?

└ Current approaches to brain-wide modeling



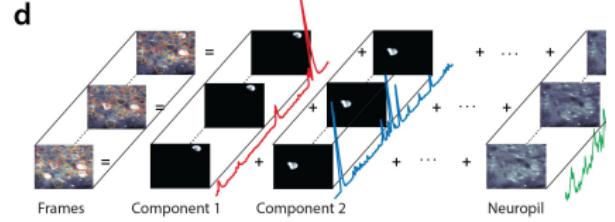
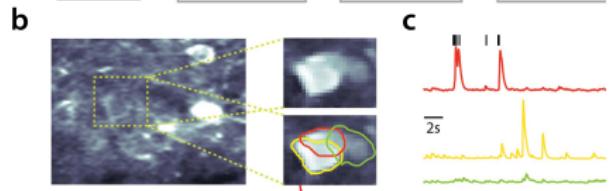
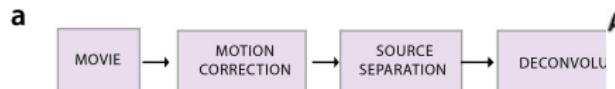
Giovannucci et al. 2019.

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Giovannucci et al. 2019.

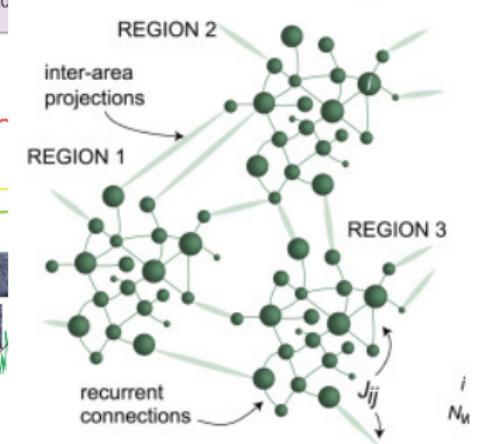
Current approaches to brain-wide modeling



Extract neuron traces

A

Neural Network Model Design



Add back spatial information

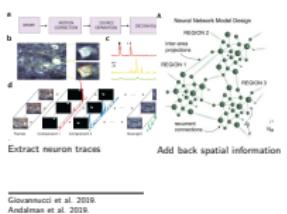
Giovannucci et al. 2019.
Andalman et al. 2019.

Aim 1: What is the most effective approach to model whole-brain data?

└ Aim 1: What is the most effective approach to model whole-brain data?

└ Current approaches to brain-wide modeling

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In general, modeling a recurrent neural network is intractable as the number of parameters grows quadratically with a number of neurons. Thus, brain-wide modeling usually involves a sparsity prior based on spatial location. In the neuroscience literature, it is not yet the norm to evaluate performance of modeling on held-out test data so we typically evaluate modeling based on how well it matches previous findings in the literature.

State-of-art volume prediction



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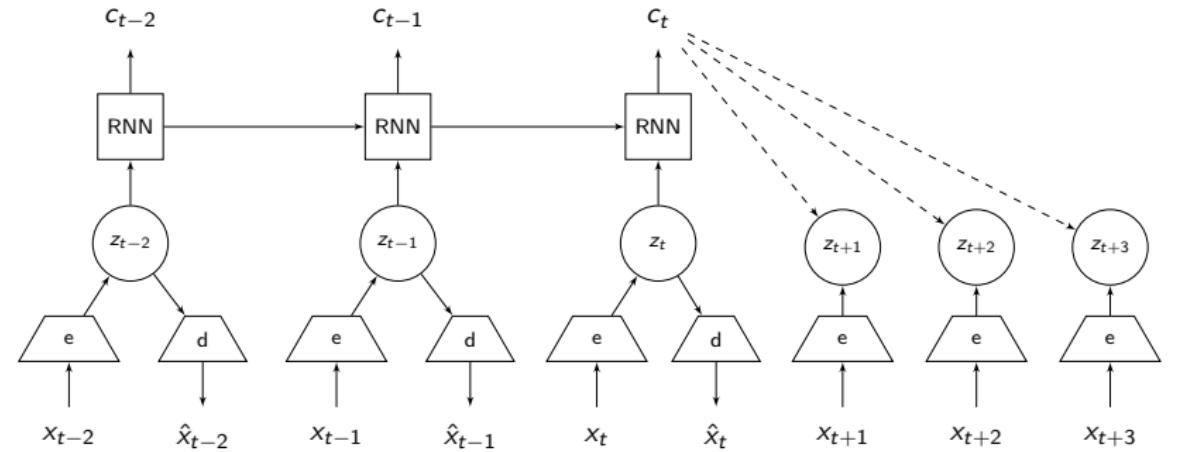
Aim 1: What is the most effective approach to model whole-brain data?
└ Aim 1: What is the most effective approach to model whole-brain data?
 └ State-of-art volume prediction



Lee, Zhang, et al. 2018

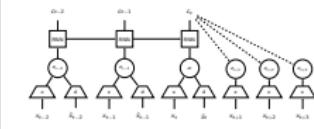
Latent-space volume prediction

Stochastic embedding



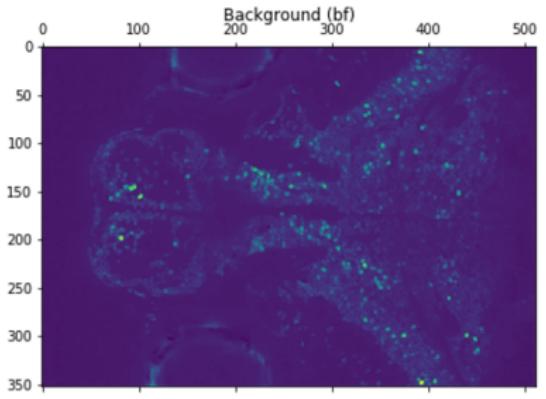
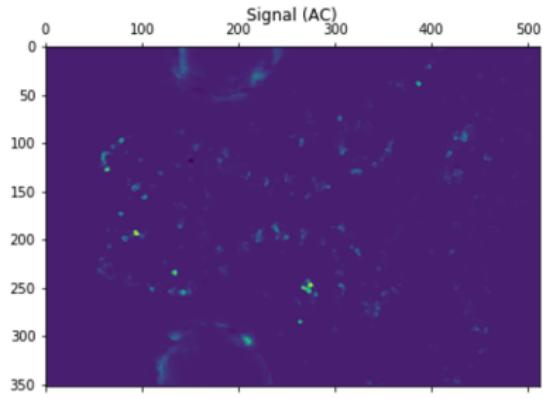
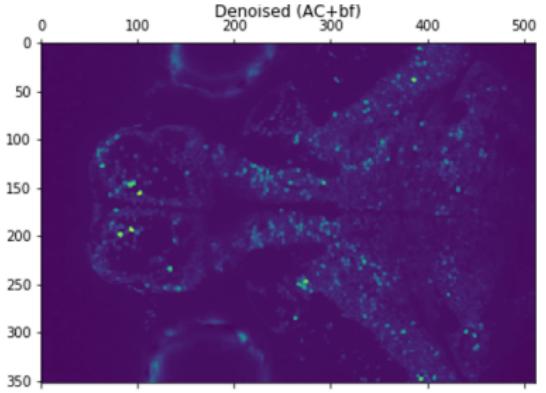
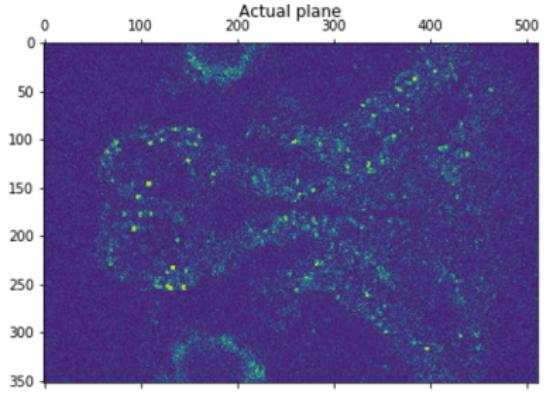
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Aim 1: What is the most effective approach to model whole-brain data?
└ Aim 1: What is the most effective approach to model whole-brain data?
 └ Latent-space volume prediction



Deep learning approach seems powerful, how well does it work? We're going to do both approaches and compare: CNMF vs raw.feedback: maybe show schematic of what is being compared?

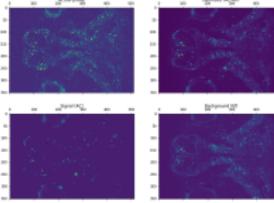
Mapping CNMF to space



Aim 1: What is the most effective approach to model whole-brain data?

└ Aim 1: What is the most effective approach to model whole-brain data?
└ Mapping CNMF to space

TODO: don't show Ac + Bf, jargon is confusing



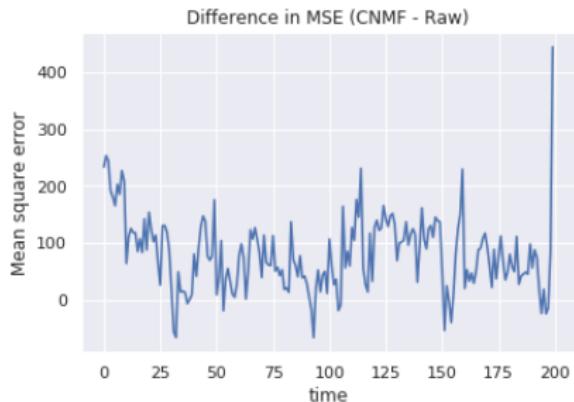
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CNMF preprocessing reduces model performance

Evaluated loss on neuron mask



show least-norm performance on top



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- Aim 1: What is the most effective approach to model whole-brain data?
 - └ Aim 1: What is the most effective approach to model whole-brain data?
 - └ CNMF preprocessing reduces model performance



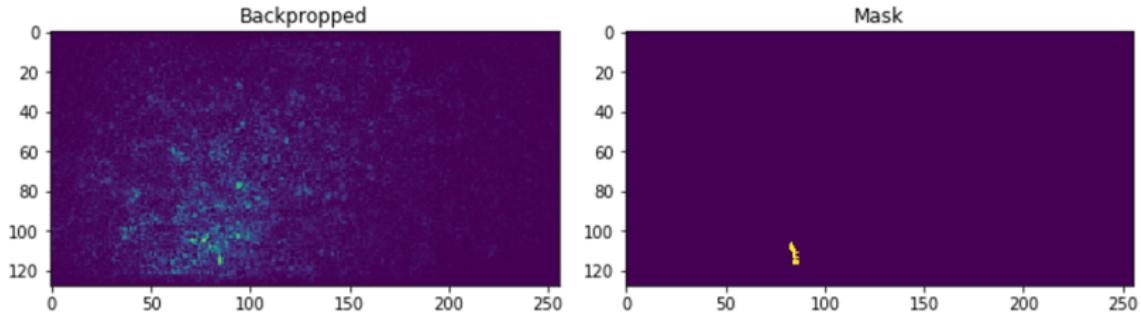
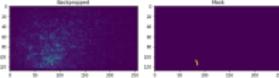
TODO need to rerun models and get rid of top chart (too confusing), show percent improvement & example frames

Model-free interpretation

Upstream connectivity



Aim 1: What is the most effective approach to model whole-brain data?
└ Aim 1: What is the most effective approach to model whole-brain data?
 └ Model-free interpretation



Ask model what is important; here we use backprop

Outline for Aim 2: How do we address the problem of underdetermination?



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Aim 2: How do we address the problem of underdetermination?
└ Aim 2: How do we address the problem of underdetermination?
 └ Outline for Aim 2: How do we address the problem of underdetermination?

Active learning, also known as optimal experiment design, is a field that concerns itself with estimating statistical models with as few experiments as possible. Existing literature deals mostly with cases where we can choose exactly what to sample; for example, OED has been deployed in the design of guide RNAs for CRISPR gene editing. In our case, we can only choose the stimuli not the entire brain state. Thus, a causal model will be essential for the penultimate application: brain state replay.

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Hypothesis: Model-based optimal experiment design will reduce underdetermination



Aim 2: How do we address the problem of underdetermination?

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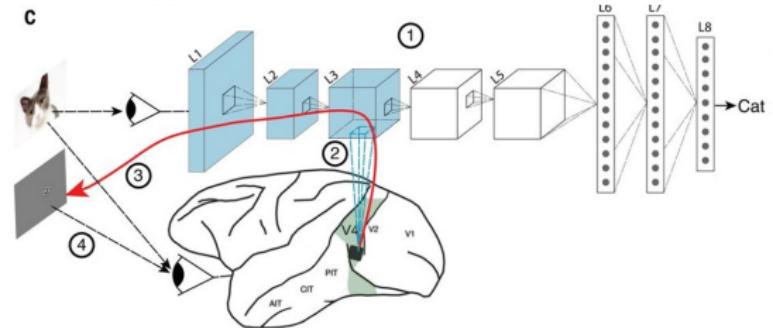
To write

To write

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Intervention → Counterfactual

one-hot control in macaque V1

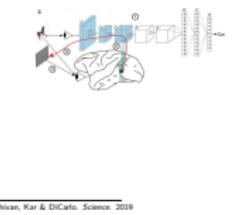


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Aim 2: How do we address the problem of underdetermination?

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└ Intervention → Counterfactual



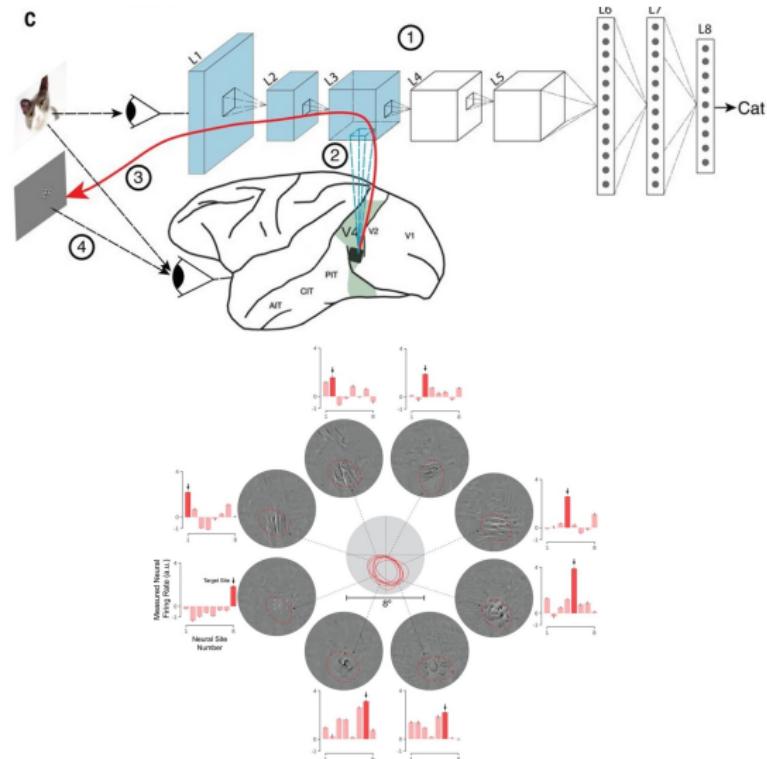
Bashivan, Kar & DiCarlo, Science, 2019

Recently, some work has been done that reaches the Counterfactual rung:
Deep Image Synthesis.

train model on imagenet, regress conv layer to macaque V1 neurons. Use
"Deep image synthesis" for one-hot population control. Example of counterfactual model-stim is very different from training! truly "imagined"

Intervention → Counterfactual

one-hot control in macaque V1



Bashivan, Kar & DiCarlo. *Science*. 2019

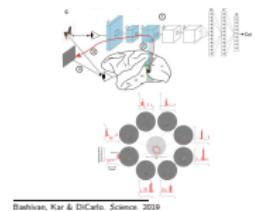
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└ Intervention → Counterfactual

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Bashivan, Kar & DiCarlo. *Science*. 2019

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Active learning introduction

Querying an oracle for classification



2019-06-13

Aim 2: How do we address the problem of underdetermination?

└ Aim 2: How do we address the problem of underdetermination?

└ Active learning introduction



1. For which photo would you ask the oracle for a label?

Active learning introduction

Querying an oracle for classification



2019-06-13

Aim 2: How do we address the problem of underdetermination?

└ Aim 2: How do we address the problem of underdetermination?

└ Active learning introduction



Mom & Dad. personal correspondence. 2016.
Instagram:atchoumthecat
Wikipedia CC BY-SA 3.0

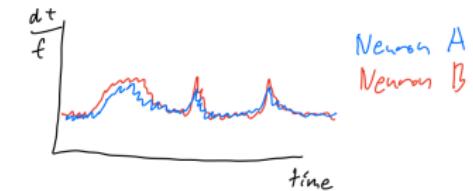


Cat

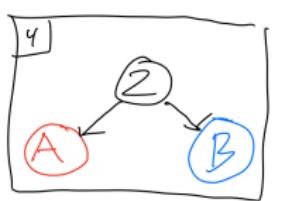
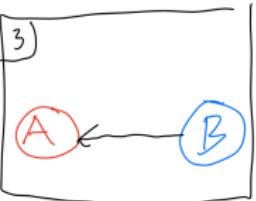
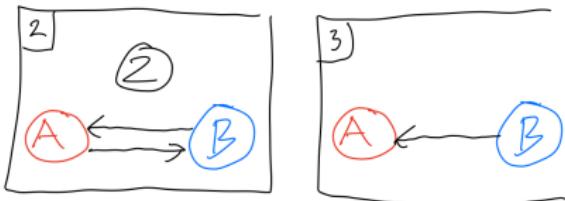
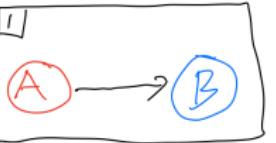
Mom & Dad. personal correspondence. 2016.
Instagram:atchoumthecat
Wikipedia CC BY-SA 3.0

Resolving correlation

single-neuron stim

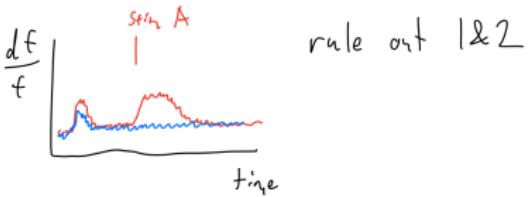


Possible models:

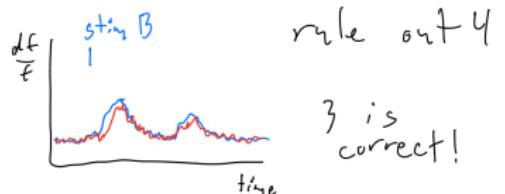


To resolve: stim A, stim B

rule out 1&2



rule out 4



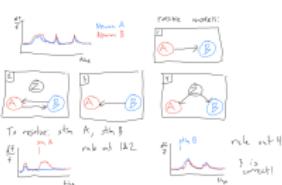
3 is correct!

Aim 2: How do we address the problem of underdetermination?

└ Aim 2: How do we address the problem of underdetermination?

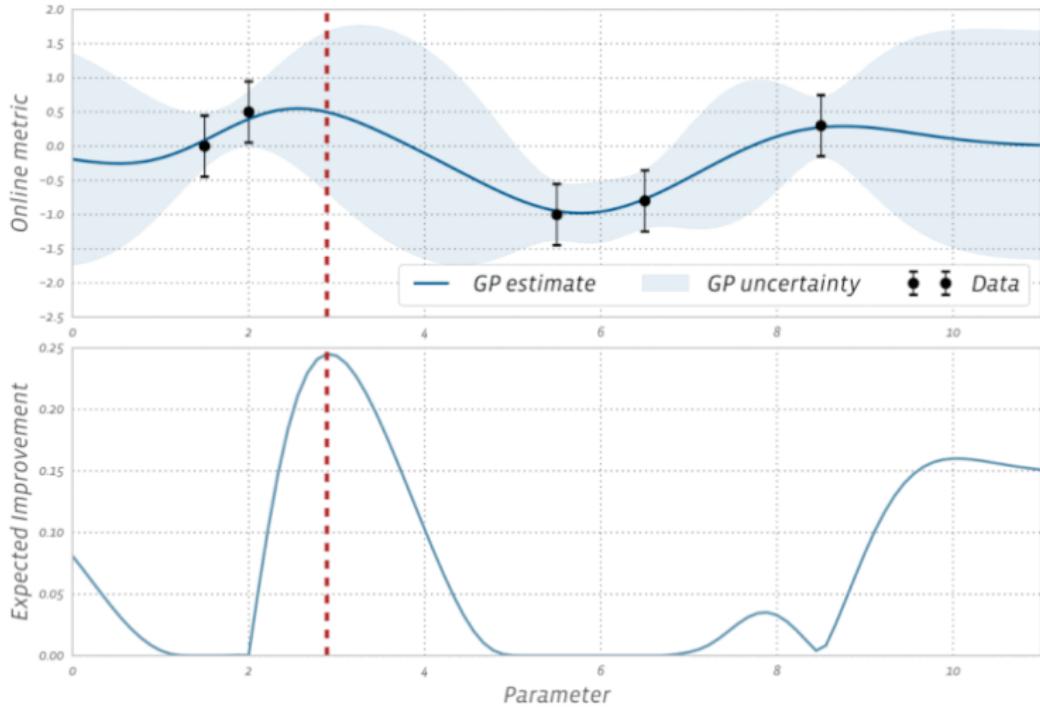
└ Resolving correlation

We discuss single neuron stim for intuition. For multi-neuron stim, easier to think in terms of latent space.



Bayesian optimization of latent space uncertainty

multi-neuron stim

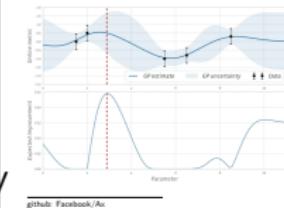


github: Facebook/Ax

Aim 2: How do we address the problem of underdetermination?

└ Aim 2: How do we address the problem of underdetermination?

└ Bayesian optimization of latent space uncertainty



Offline optimal experiment design



Data collection:

- 1 Acquire resting state / experiment of interest data
- 2 N trials of random single-cell perturbation
- 3 Acquire resting state / experiment of interest data

Data analysis:

- ▶ train on [1]
- ▶ choose $k \ll N$ from [2]
- ▶ Test on [3]

How much better can we do by choosing k vs random k in terms of test performance on [3]

Aim 2: How do we address the problem of underdetermination?

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└ Offline optimal experiment design

2019-06-13

Data collection:
1 Acquire resting state / experiment of interest data
2 N trials of random single-cell perturbation
3 Acquire resting state / experiment of interest data

Data analysis:
▶ train on [1]
▶ choose $k \ll N$ from [2]
▶ Test on [3]

How much better can we do by choosing k vs random k in terms of test performance on [3]

Online optimal experiment design



2019-06-13

Data collection:

- 1 Acquire resting state / experiment of interest data
- 2 choose each stimulation pattern sequentially during resting state / experiment of interest
- 3 random Stim during resting state / experiment of interest data

How well can we predict [3] by training on just [1] or [2]?

Aim 2: How do we address the problem of underdetermination?

└ Aim 2: How do we address the problem of underdetermination?

 └ Online optimal experiment design

Data collection:

- 1 Acquire resting state / experiment of interest data
 - 2 choose each stimulation pattern sequentially during resting state / experiment of interest
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- How well can we predict [3] by training on just [1] or [2]?

Brain state replay



2019-06-13

Aim 2: How do we address the problem of underdetermination?

└ Aim 2: How do we address the problem of underdetermination?
└ Brain state replay

Data collection:

- 1 Acquire brain trajectory of interest
- 2 choose each stimulation pattern sequentially during resting state / experiment of interest
- 3 Stim brain to keep observations in line with [1]

How well can we track a previously observed trajectory?

Outline for Aim 3: Do the model substructures map to underlying biology?



Motivation

Aim 1: What is the most effective approach to model whole-brain data?

Aim 2: How do we address the problem of underdetermination?

Aim 3: Do the model substructures map to underlying biology?

2019-06-13

Aim 3: Do the model substructures map to underlying biology?
└ Aim 3: Do the model substructures map to underlying biology?
└ Outline for Aim 3: Do the model substructures

Motivation

Aim 1: What is the most effective approach to model whole-brain data?

Aim 2: How do we address the problem of underdetermination?

Aim 3: Do the model substructures map to underlying biology?

1. Aim 1&2 are about what we can do with best-in-class models; aim 3 is about simplifying the model / making more biologically compatible. Less complexity but simpler. How close in performance can we get to "gold standard" model from Aim 1 & 2?
2. First, we introduce prior work on functional motif discovery via optogenetics.
3. Next, I will discuss possible biological priors and constraints

Hypothesis: Enforcing causal biological constraints will improve model performance while aiding



Aim 3: Do the model substructures map to underlying biology?
└ Aim 3: Do the model substructures map to underlying biology?
 └ Hypothesis: Enforcing causal biological

2019-06-13

1. Requiring model to predict *in situ* hybridization allows for interpretation of cell-type contribution to dynamics
2. Template-based representations allow for unsupervised learning of purported circuit motifs

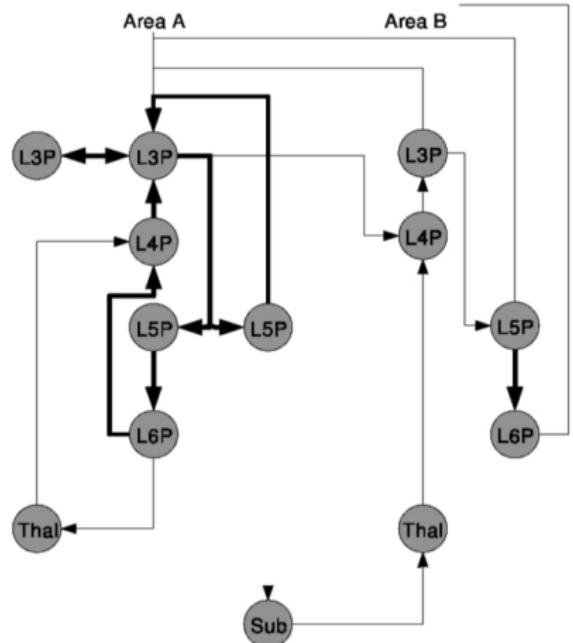
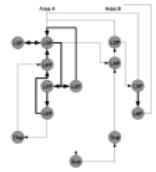
1. Requiring model to predict *in situ* hybridization allows for interpretation of cell-type contribution to dynamics
2. Template-based representations allow for unsupervised learning of purported circuit motifs

Canonical circuits

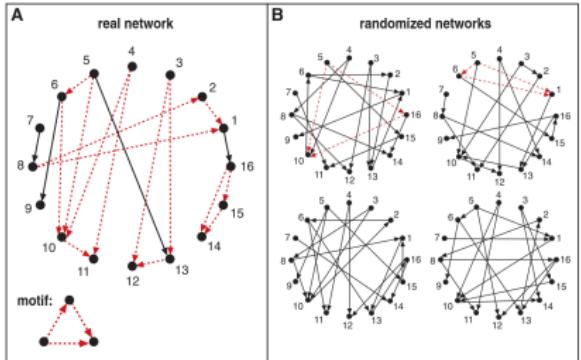


Aim 3: Do the model substructures map to underlying biology?
└ Aim 3: Do the model substructures map to underlying biology?
 └ Canonical circuits

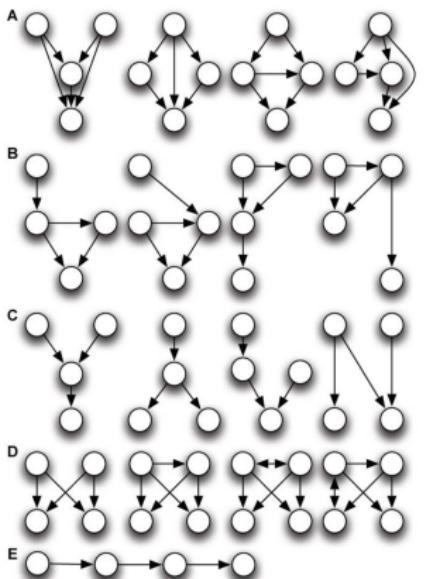
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Network motifs



Schematic illustrating an over-represented motif



Over-represented motifs from *C. elegans* connectome

Milo et al 2002
Qian et al 2011

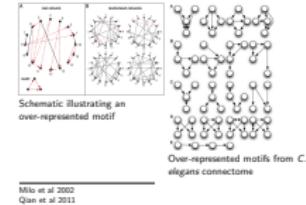
Aim 3: Do the model substructures map to underlying biology?

└ Aim 3: Do the model substructures map to underlying biology?

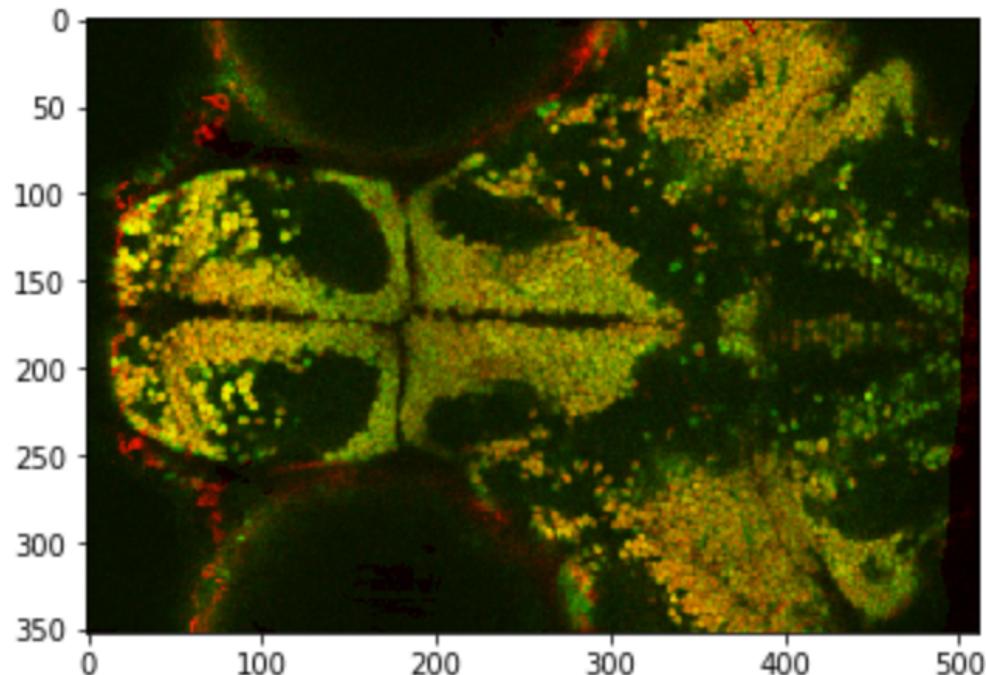
└ Network motifs

For a stringent comparison, we used randomized networks that have the same single-node characteristics as does the real network: Each node in the randomized networks has the same number of incoming and outgoing edges as the corresponding node has in the real network.

A: nested feed-forward motifs, B: feed-forward motifs with entry and exit, C: integrations and bifurcations, D: bi-fan motif with or without coupling of the inputs, and E: linear chains.



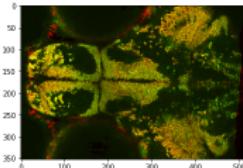
in situ cell type identification



2019-06-13

- Aim 3: Do the model substructures map to underlying biology?
 - └ Aim 3: Do the model substructures map to underlying biology?
 - └ *in situ* cell type identification

placeholder. Talk about colored graphs, predicting cell type, etc. Note that this photo is actually alive (isosbestic) GCamp6s to fixed GCaMP6s



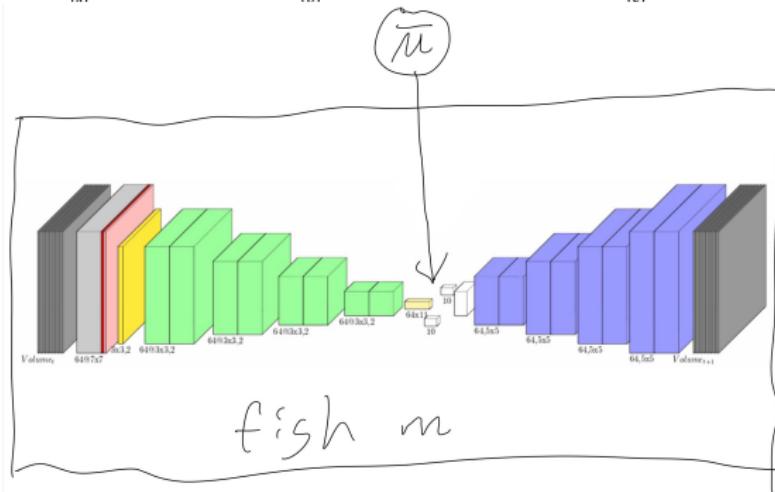
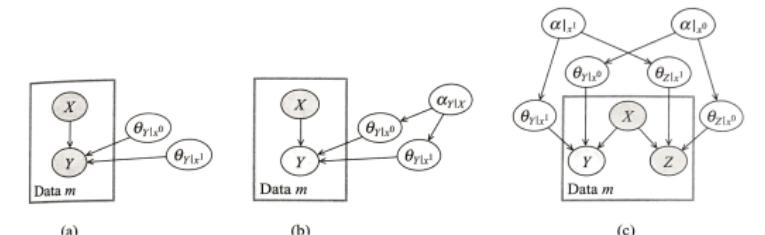
Extracting principles from multiple fish



Aim 3: Do the model substructures map to underlying biology?

- Aim 3: Do the model substructures map to underlying biology?

└ Extracting principles from multiple fish



Koller & Friedman. *Probabilistic Graphical Models*. 2009.

Aim 3: Do the model substructures map to underlying biology?

Tyler Benster, Qualifying Exam

