# Modeling Dynamics on a Canonical Neural Manifold in C. *elegans*

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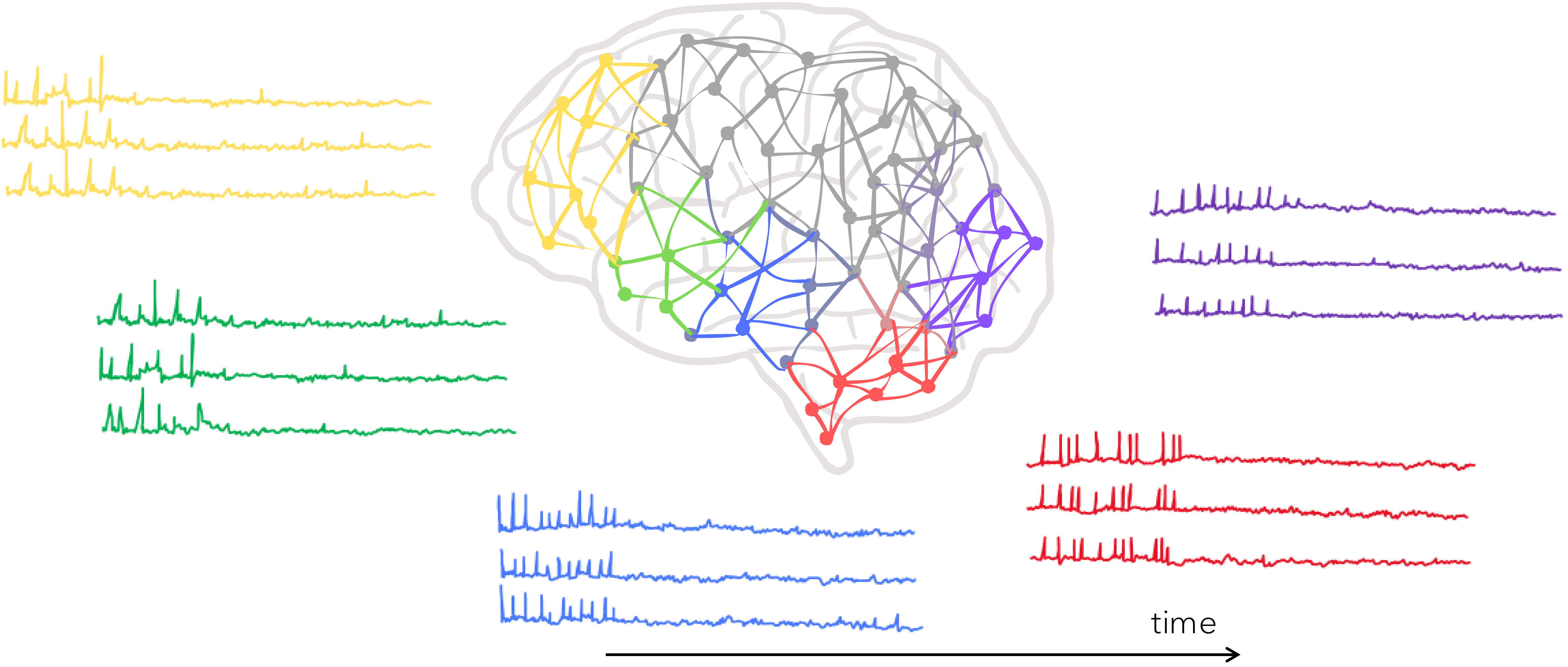
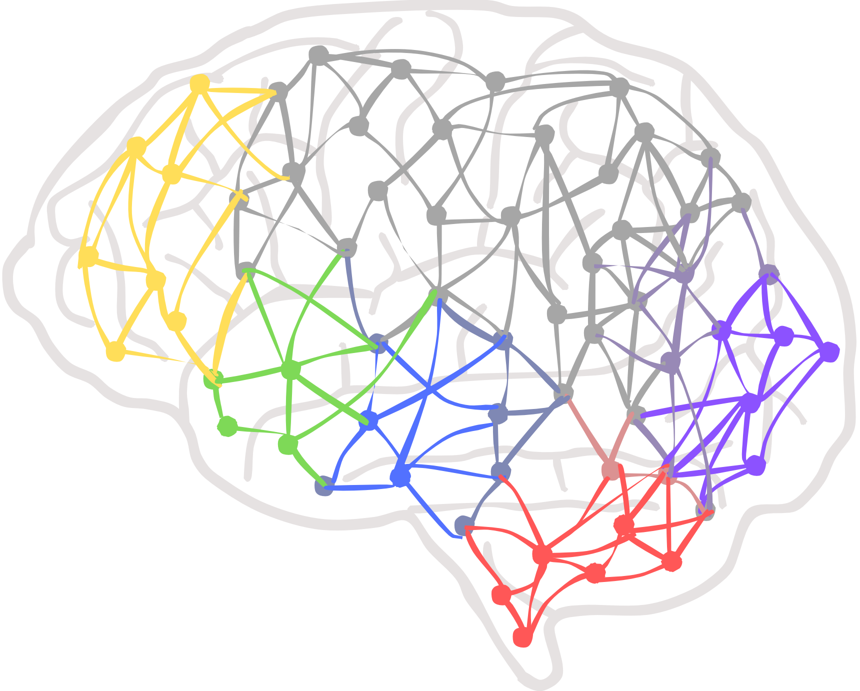
# The unit of computation is the neural population

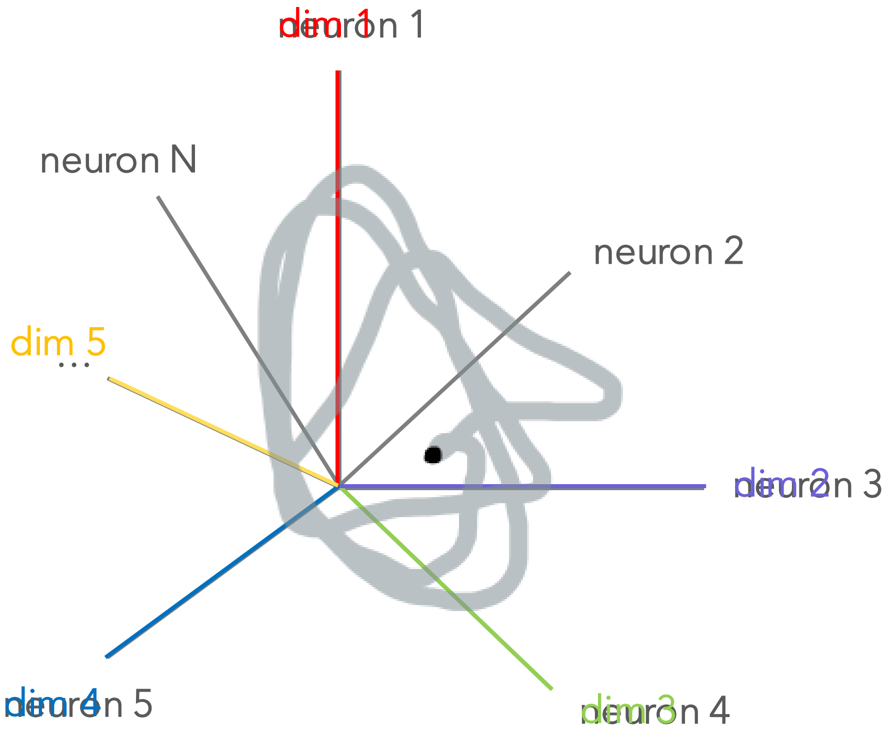



neural population =
a collection of neurons with correlated activity

neural dynamics = interaction of neurons over time

# From the population doctrine to a reduced neural state space






neural manifold

# Neural state evolution is given by dynamical functions

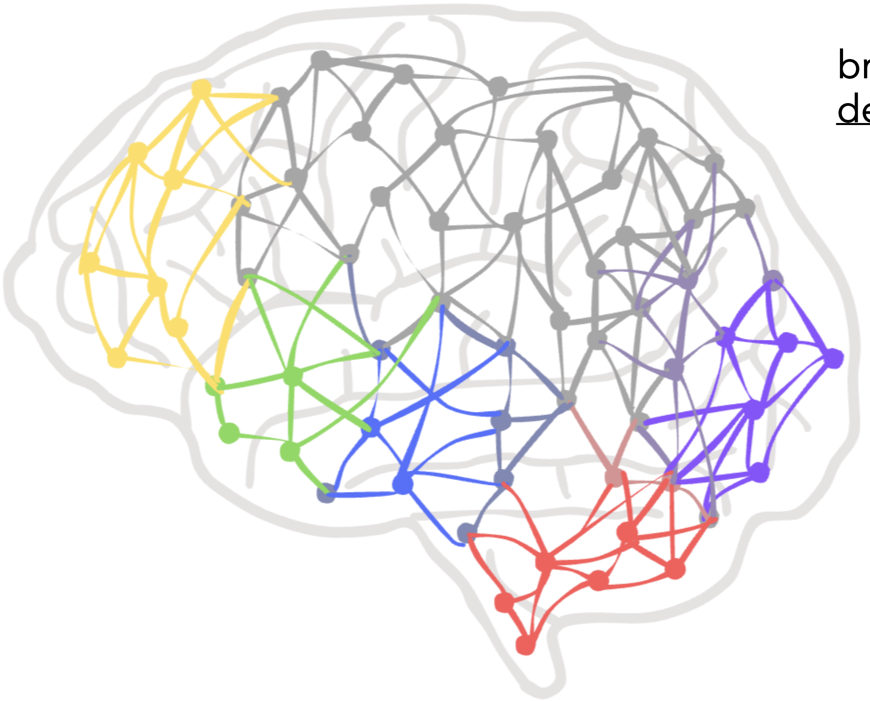
**well-studied**

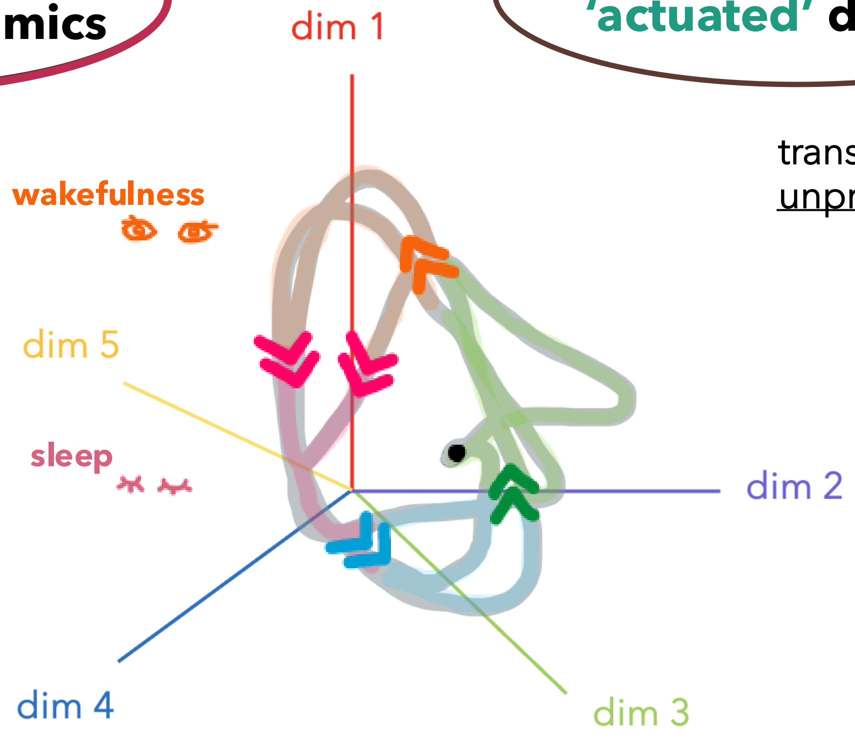
**autonomous**
**'intrinsic' dynamics**

brain is moved in a
deterministic way

**non-autonomous**
**'actuated' dynamics**

transitions are
unpredictable!






neural manifold displays
latent states

# How can we build a model of these dynamical functions?

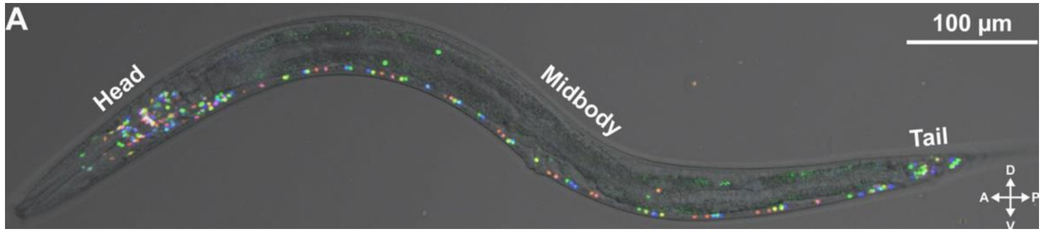
How can we capture non-autonomous, actuated dynamics alongside the autnomous ones?

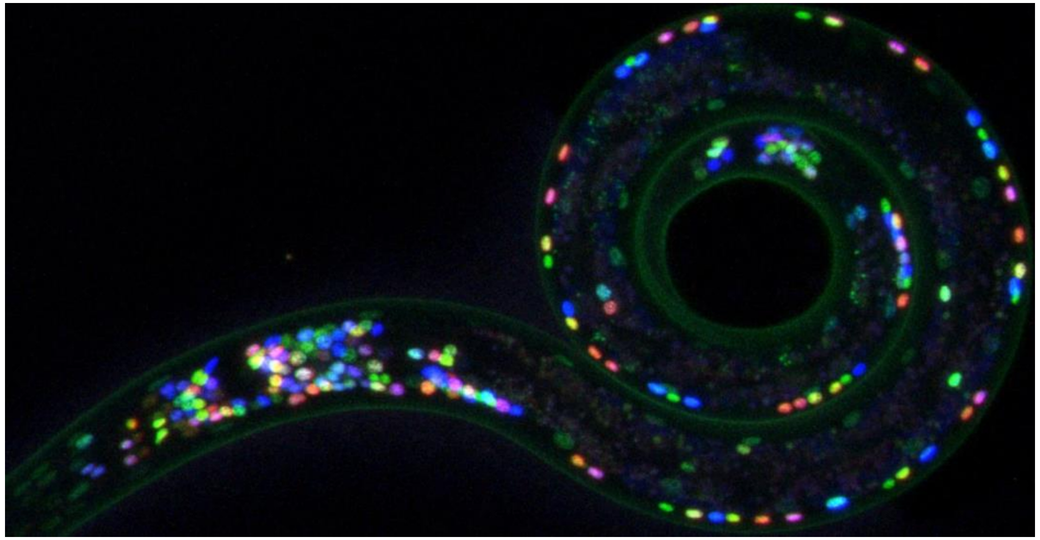
What are the steps required to create a neural manifold that is consistent across individuals?

Getting whole brain recordings is challenging!

We know a lot about C. elegans:
Connectome, Biophysical properties,..

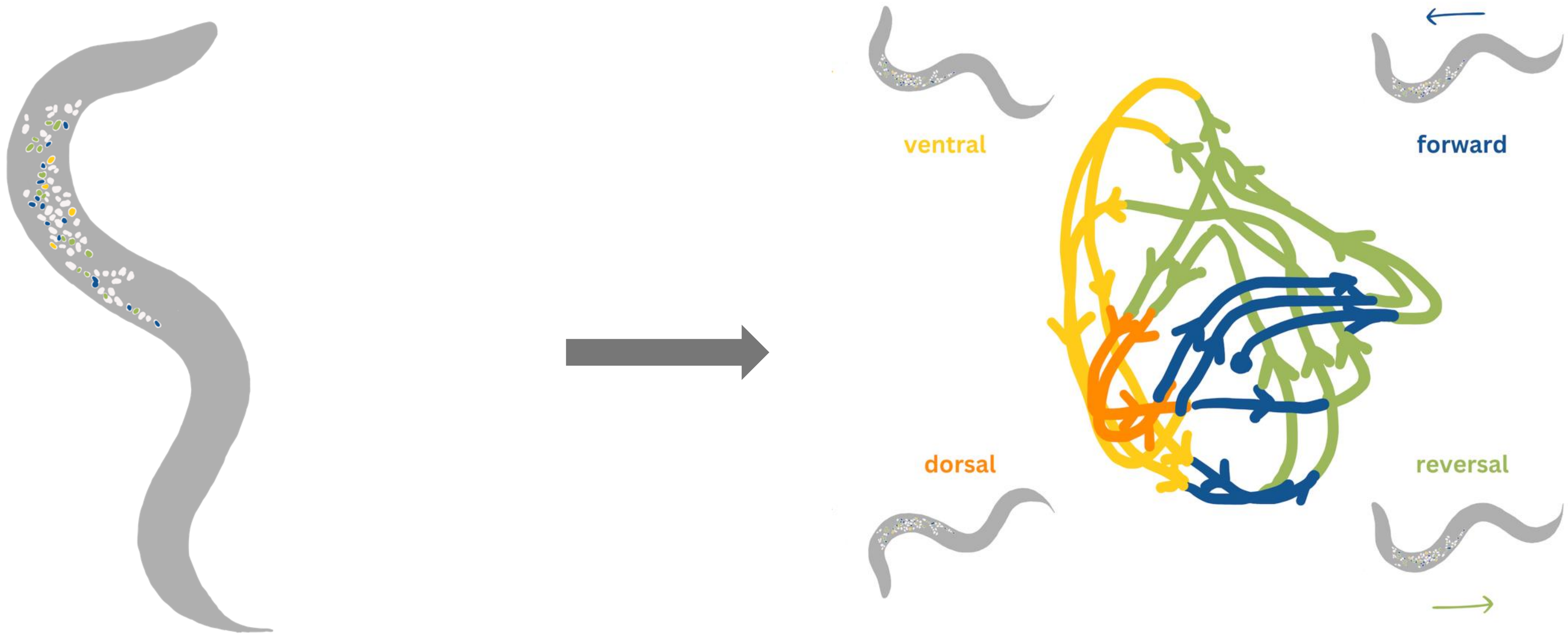
*Horbert Lab*



*Caenorhabditis elegans* = a nematode with 302 fully mapped neurons

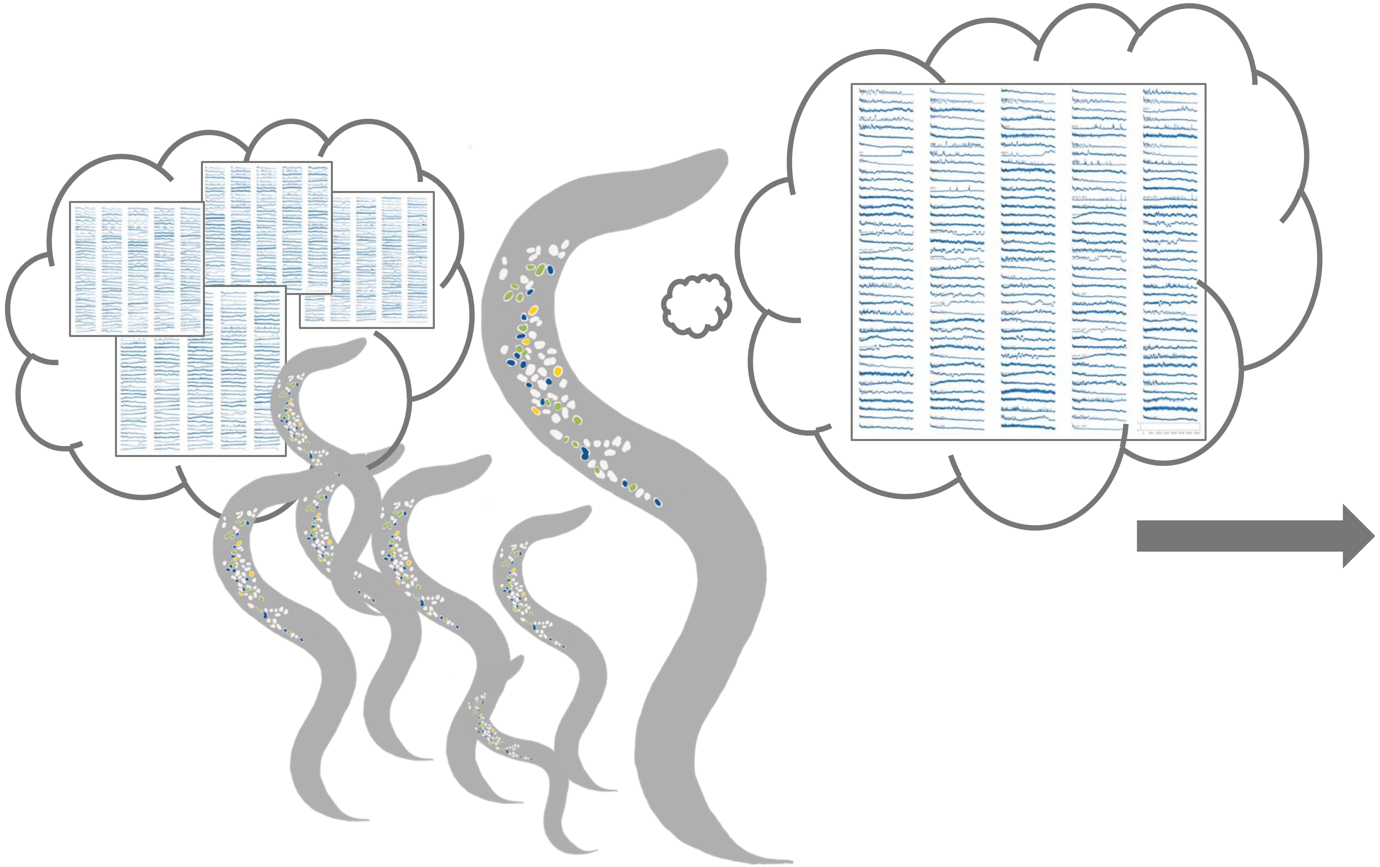
# In search of a neural manifold for C. *elegans*




Major behaviors of *C. elegans* are embedded in low-dimensional manifold structures.
*Adapted from Kato et al., 2015.*

Does this structure exhibit properties that apply 'universally' to all C. *elegans* individuals?

# What if we align whole brain recordings to construct a canonical neural manifold?





Thanks to Rebecca Kresnik and Kerem Uzel for the data!

Data Alignment opens a can of worms due to inconsistencies in..

→ frame rate
→ settings of laser power
→ number of neurons identified

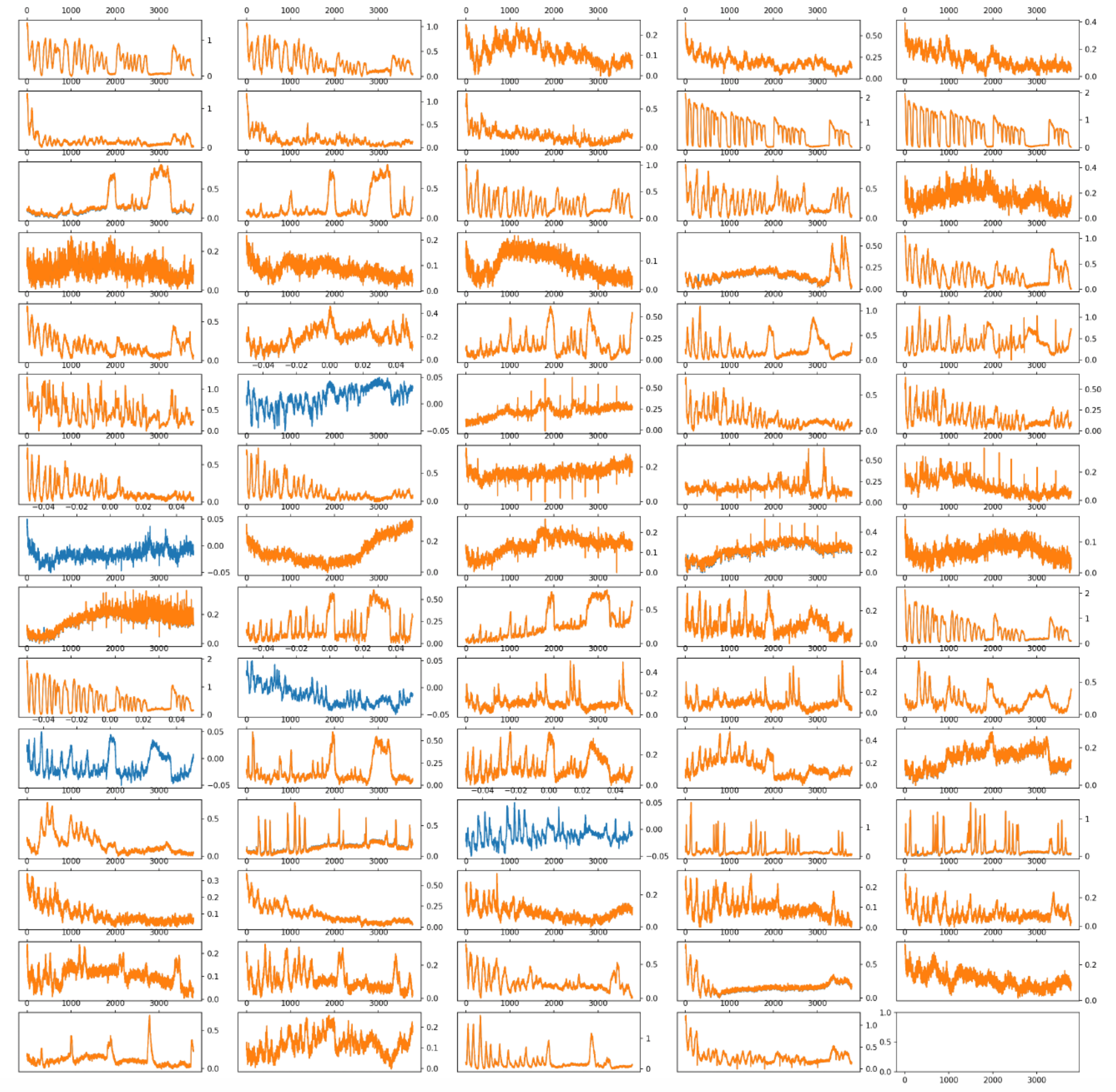
# Methods for Data Preprocessing

Up- and Downsampling

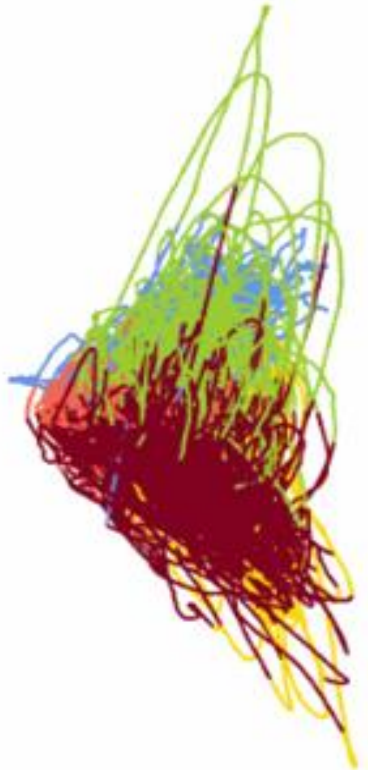
Quartile Normalization

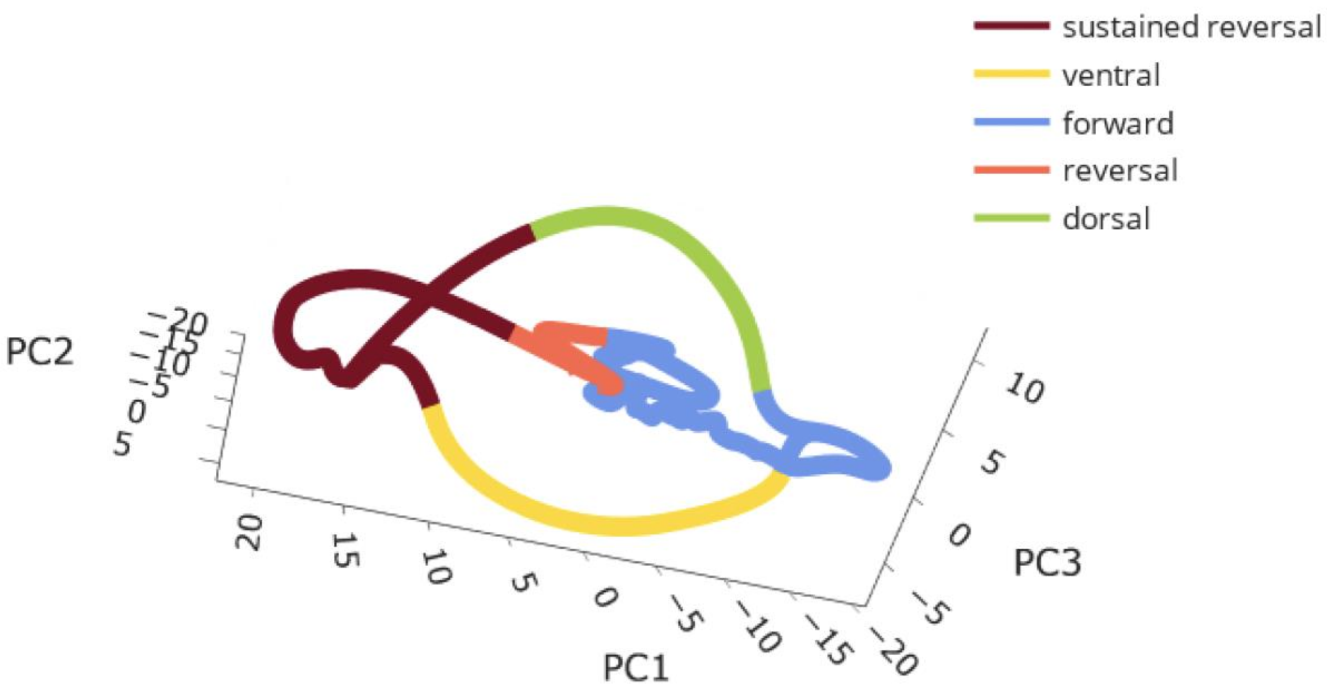
Data Imputation

**Probabilistic Principal Component Analysis**



# A PCA-based low-dimensional representation of 23 whole-brain recordings shows a manifold-like structure

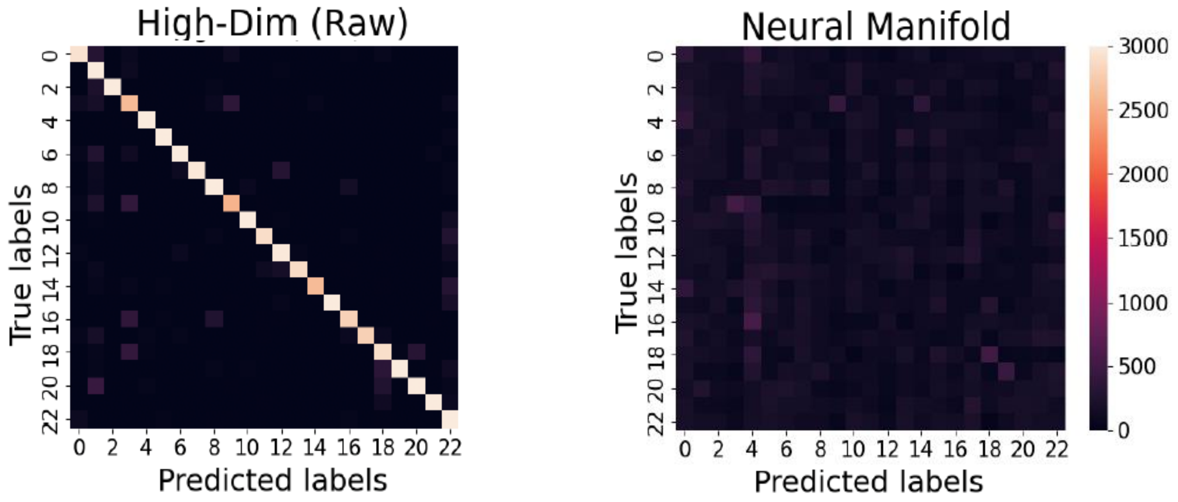





the manifold can be separated by behavior..
and should not be separated by individuality

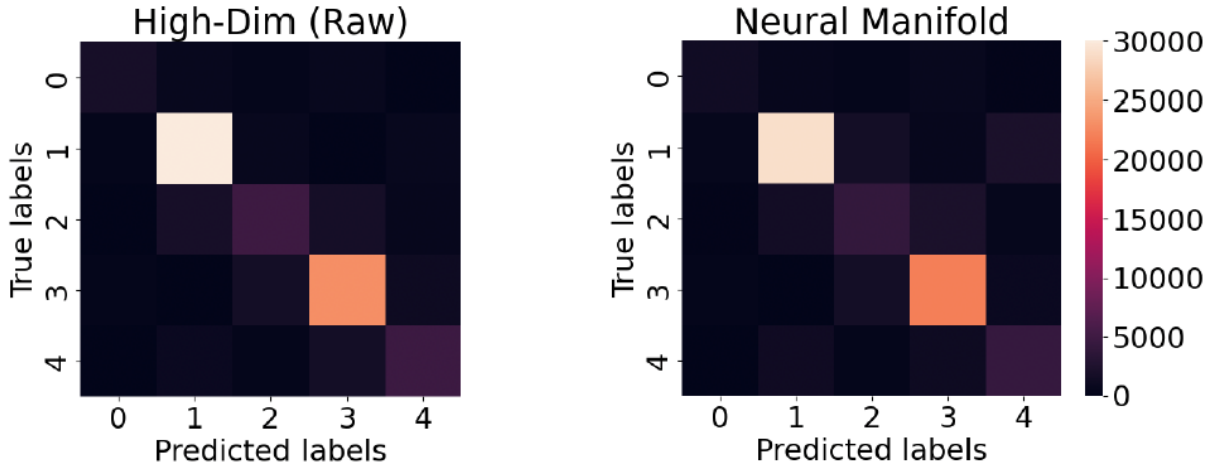
# While the neural manifold shows decreased variability caused by individuality..

dataset membership




# it still successfully separates behavior states

behavior state annotation



# Many existing models of the (non-) autonomous dynamics

**Dynamical Systems**

$$x_{t+1} = Ax_t$$

**simple**

interpretable

**rSLDS** (Linderman et al. 2016)

**DMDc** (Fieseler et al. 2020)

**We are here**

**LFADS** (Sussilo et al. 2016)

**iLQR-VAE** (Schimel et al. 2022)

**Neural Networks**

$$f\left(b + \sum_{i=1}^{n} x_i w_i\right)$$

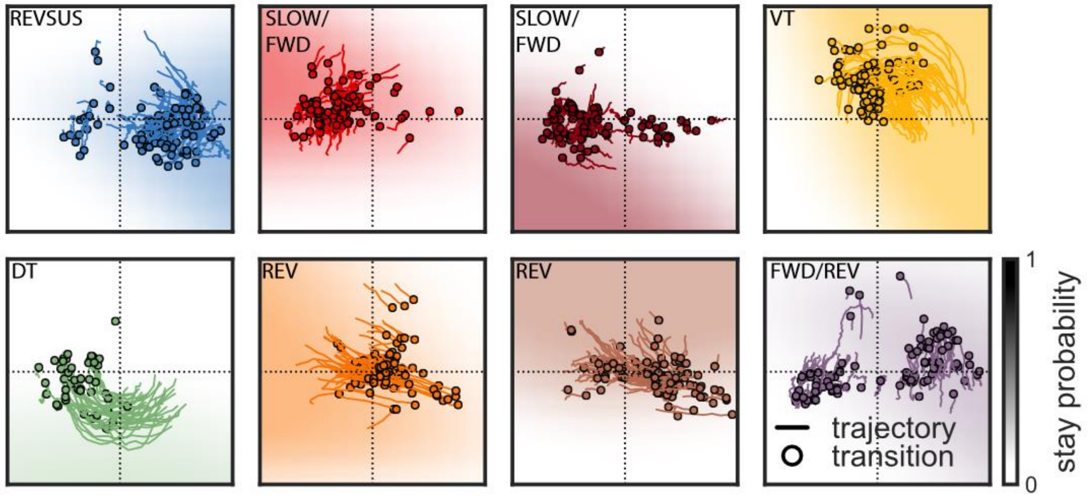
**complex**

uninterpretable

**DKF** (Krishnan et al. 2015)

# Dynamical Systems Models

latent subsystems don't overlap in time?



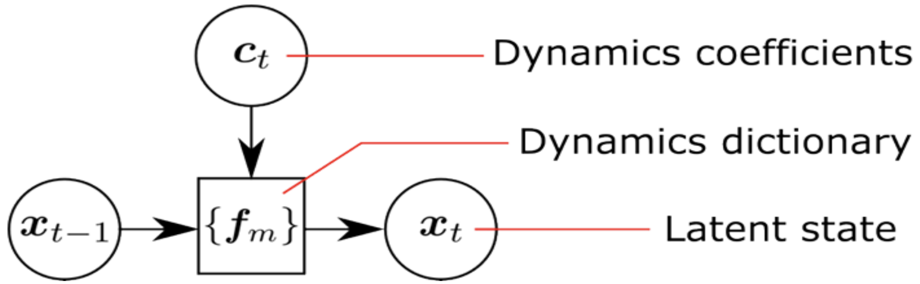

*Hierarchical recurrent state space models reveal discrete and continuous dynamics of neural activity in C. elegans, Linderman et al.*

Complex nonlinear dynamics can be broken into simpler linear dynamics

A linear dynamical system corresponds to a latent state

Mudrik et al. (2022): **neural activity at a given time point is given by a time-varying <u>linear combination of these linear dynamical systems</u>**

**Decomposed Linear Dynamical System (dLDS)**

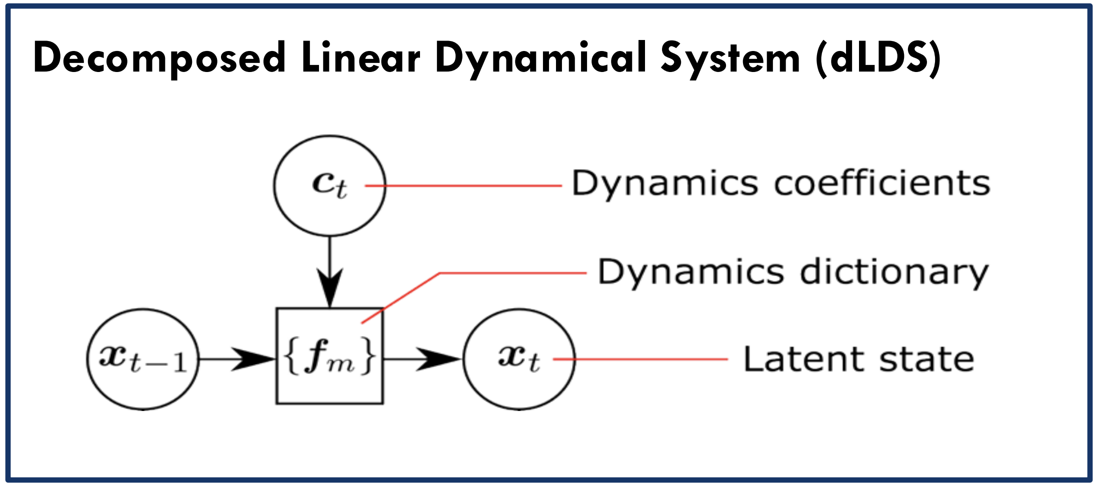


# The good and the bad of dLDS

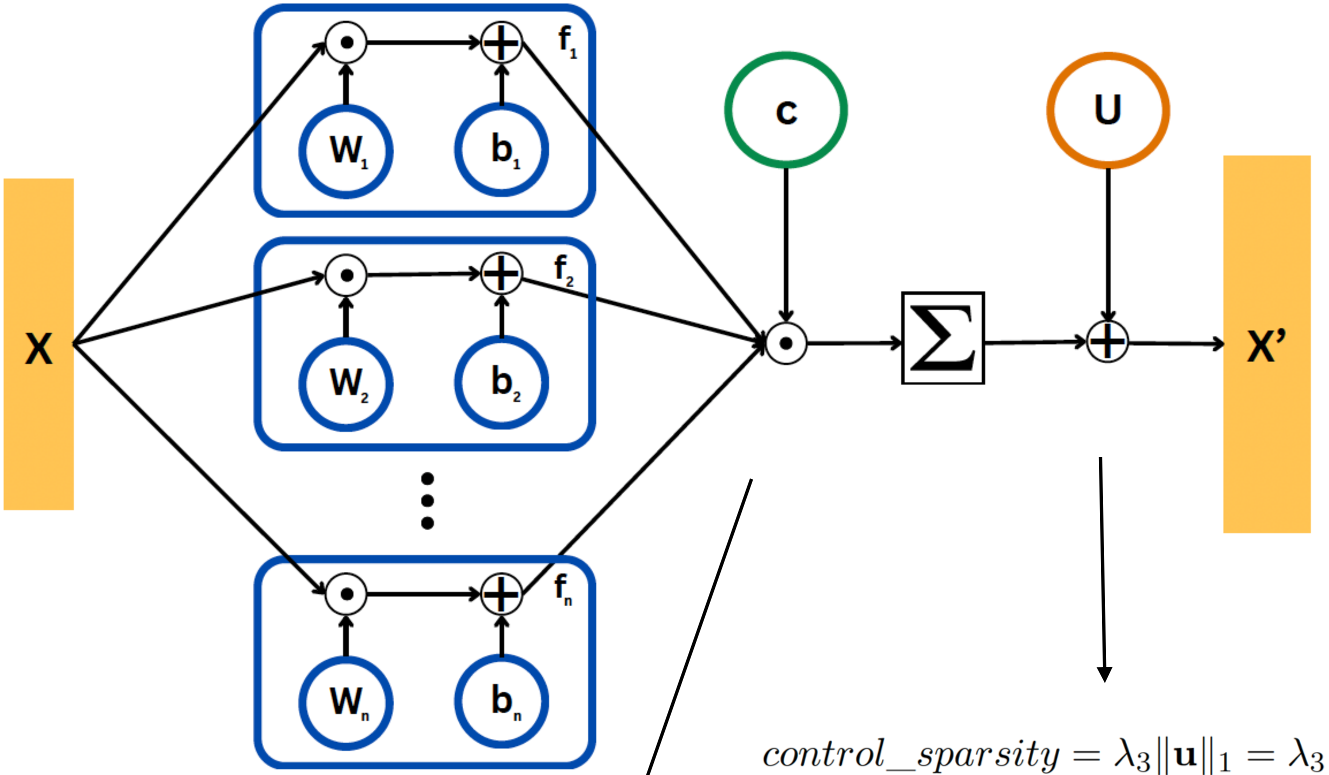
**Advantage**: interpretable model components (coefficients)

**Disadvantages**: autonomous system (does not capture actuation), iterative algorithm (slow)

**Solution:** Gradient Descent, Control Theory $x_{t+1} = Ax_t \longrightarrow x_{t+1} = Ax_t + Bu_t$



# cdLDS: Reformulating dLDS as a feed-forward Neural Network to incorporate control signal inference




$$control\_sparsity = \lambda_3 \|\mathbf{u}\|_1 = \lambda_3 \sum_{i=1}^{d} |u_i|$$

$$sparsity = \lambda_1 \|\mathbf{c}\|_1 = \lambda_1 \sum_{i=1}^{d} |c_i|$$

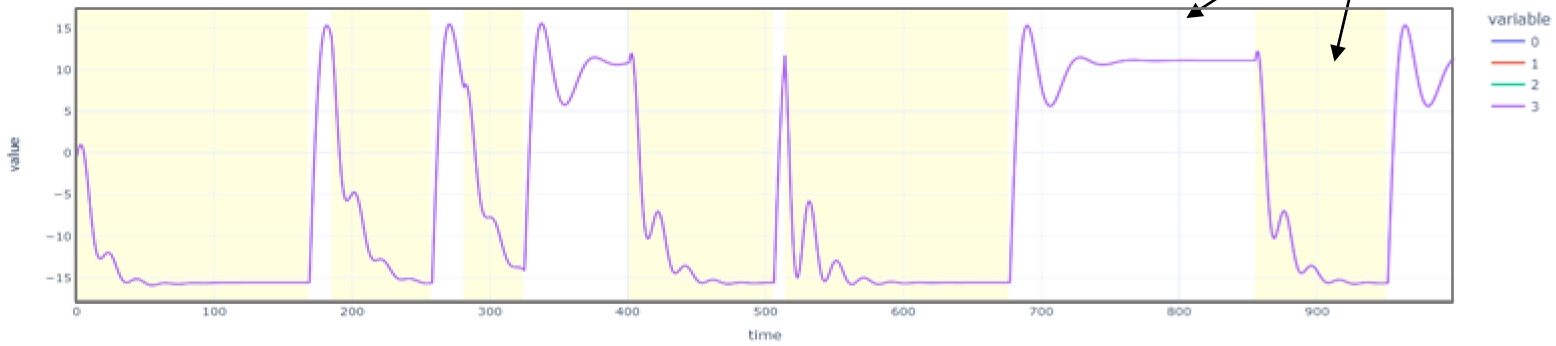
$$smoothness = \lambda_2 \|(\mathbf{c}_{t+1} - \mathbf{c}_t)\|_2 = \lambda_2 \sqrt{\sum_{i=1}^{d} (c_{i+1} - c_i)^2}$$

$$MSE = \frac{1}{d} \sum_{i=1}^{d} (x_{i+1} - \hat{x}_{i+1})^2$$

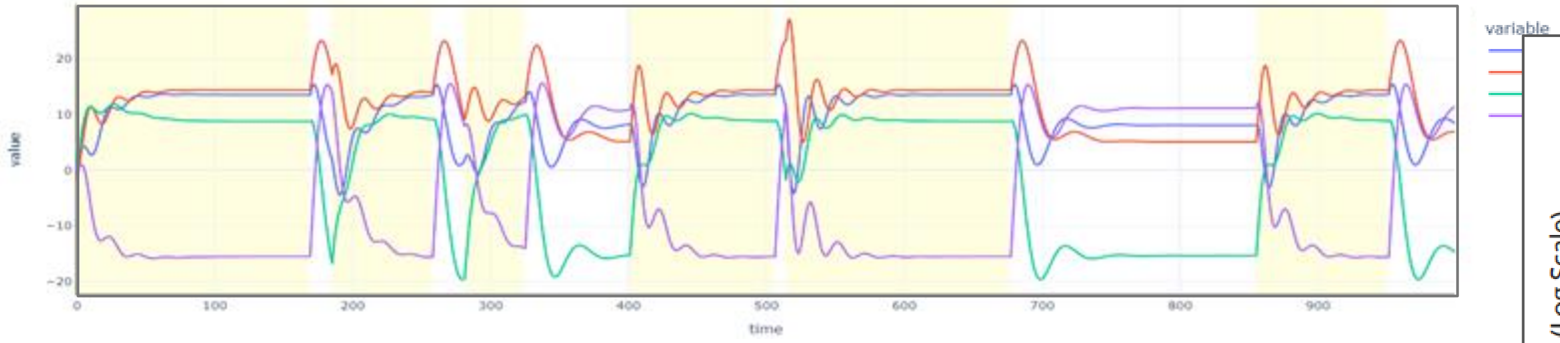
# cdLDS – Model Validation/Testing

different dynamics from 2 systems

1. Generate synthetic data



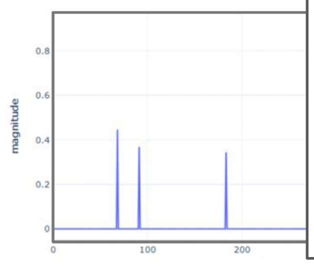

Synthetic Data from a two state system

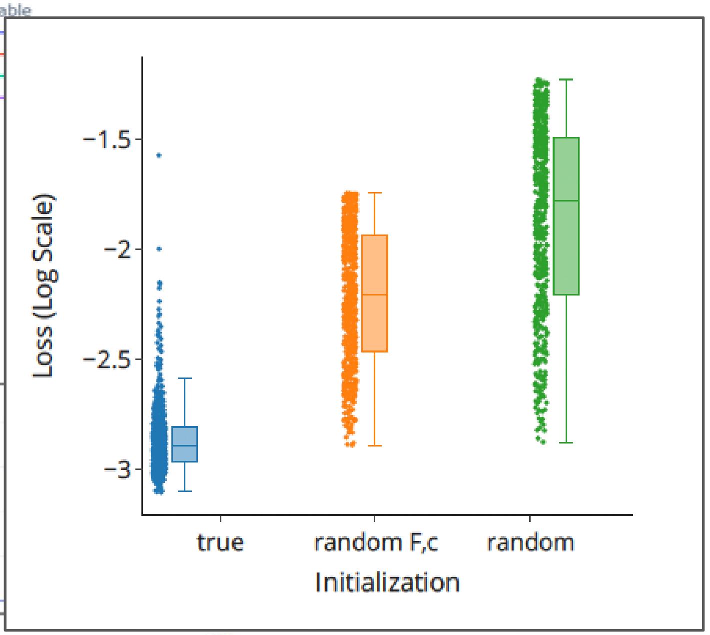



2. Initialize Model components with Ground Truth

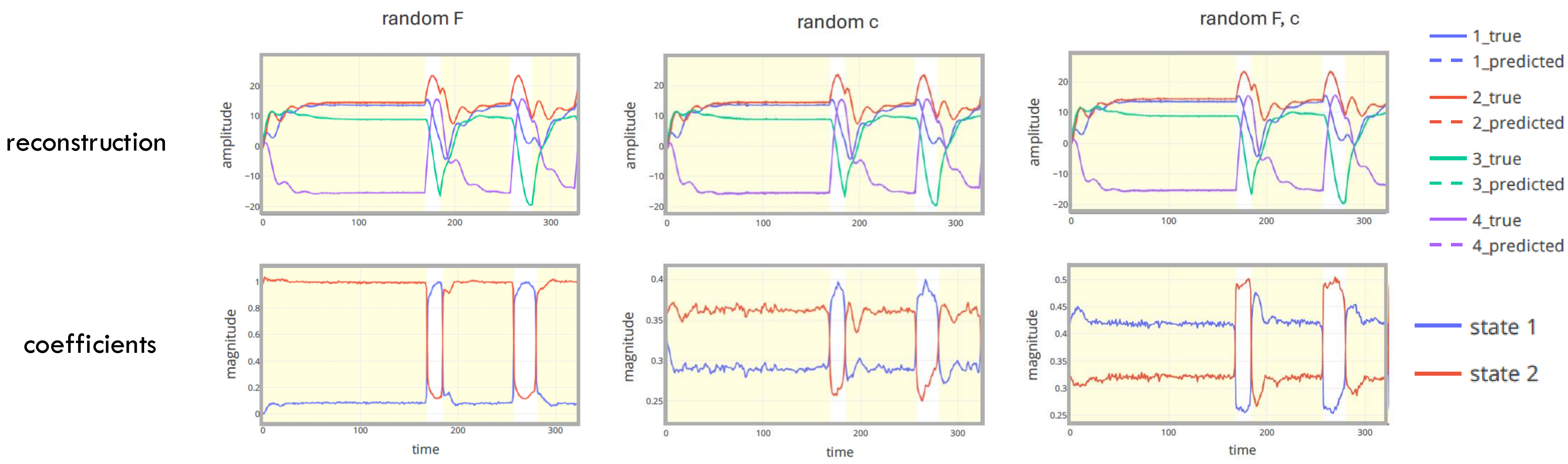
3. Sweep over hyperparameters

Control Signals



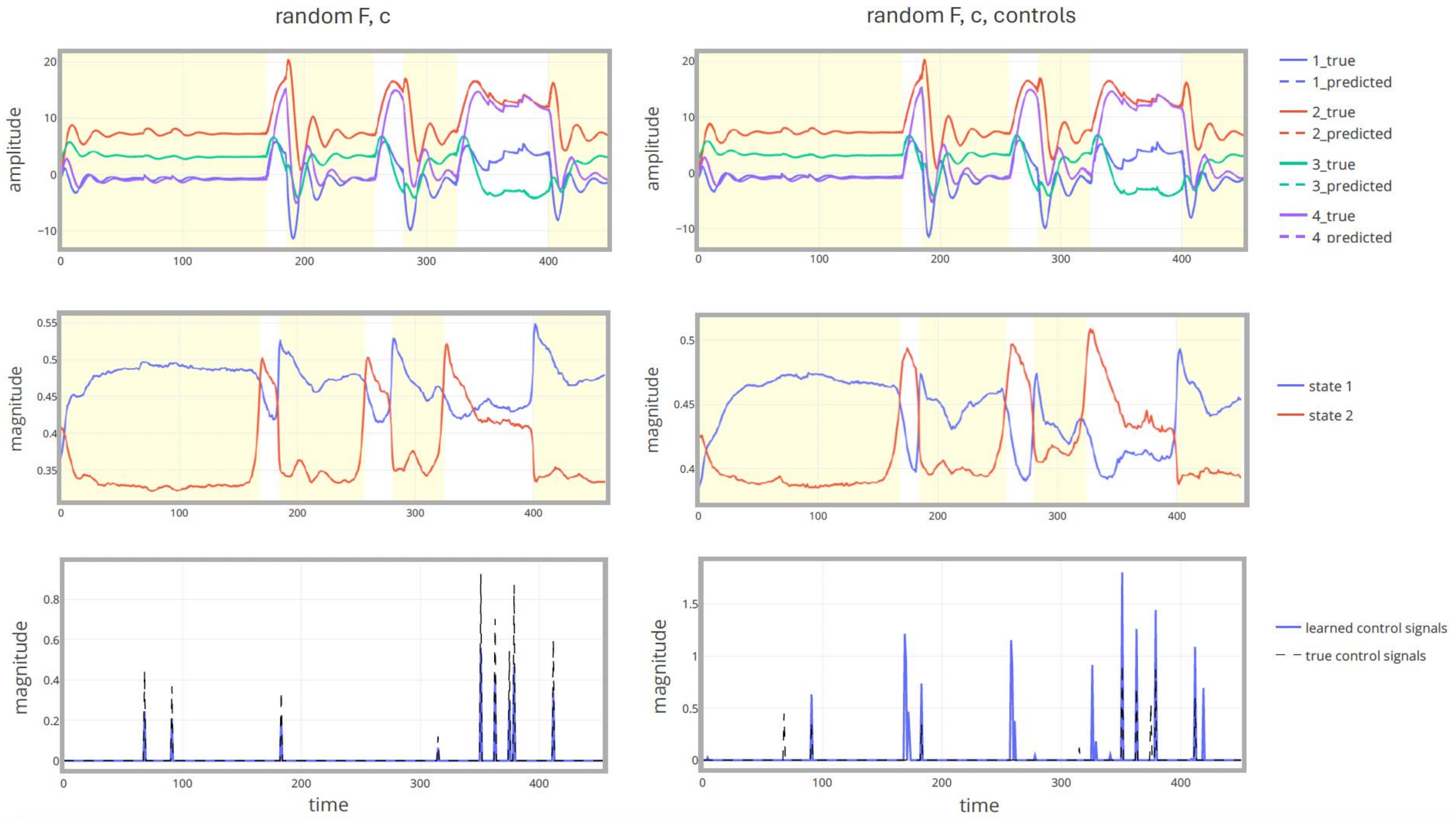



# dLDS accurately infers model coefficients in synthetic data



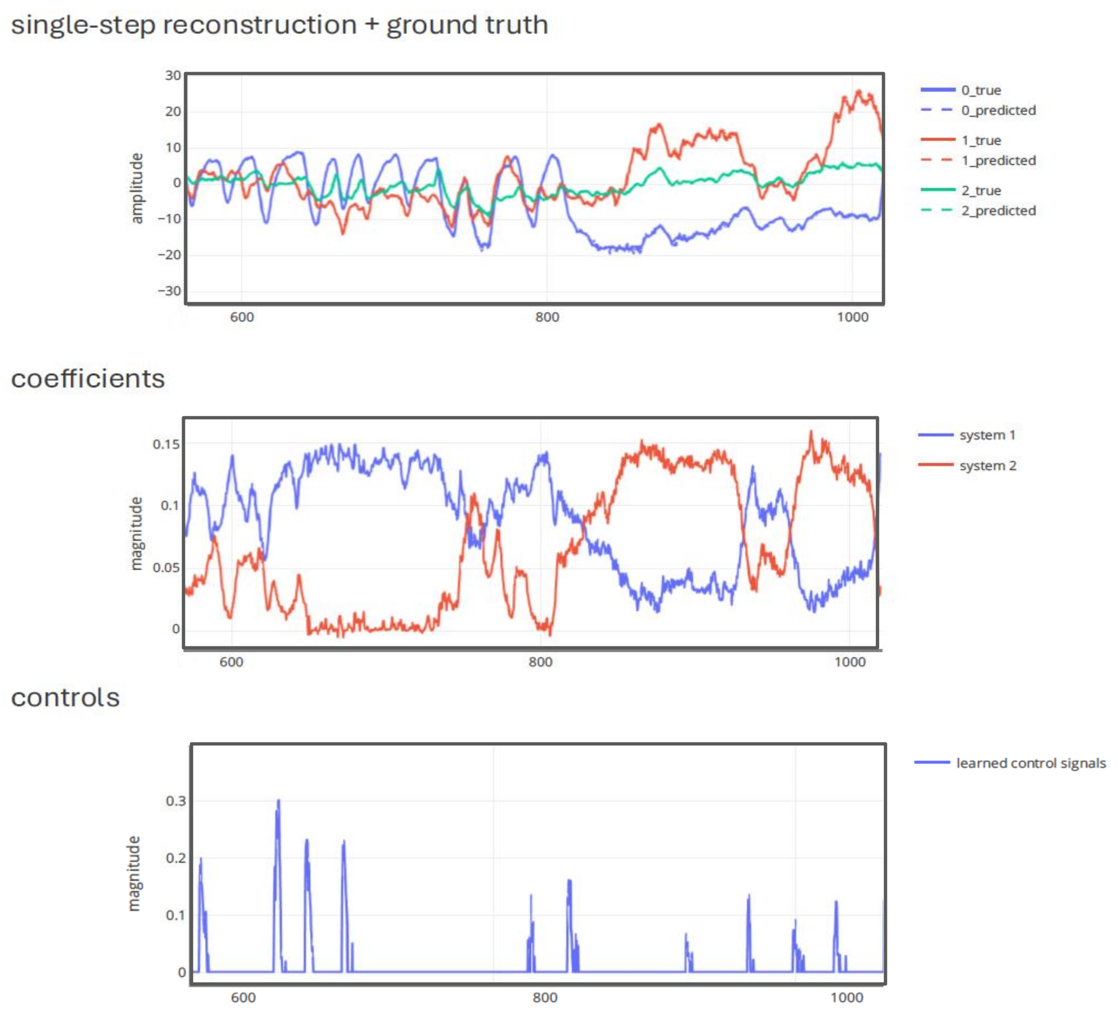

dLDS with true components applied to toy data retains the true coefficients.

# cdLDS disambiguates control signals from the coefficients in synthetic data




cdLDS applied to toy data yields coefficients and control signals close to their true counterparts.

# cdLDS applied to the canonical neural manifold consistently separates coefficients and control signals




**cdLDS with a control initialization strategy applied to a single recording projected to the canonical neural manifold.**

# Conclusion and Outlook

**canonical neural manifold**
→ a low-dimensional manifold structure from 23 *C. elegans* individuals
→ a *C. elegans* latent state space (that is already used for modeling)
→ a pipeline of preprocessing steps to align neural activity data

**controlled decomposed linear dynamical systems (cdLDS)**
→ PoC, disambiguation intrinsic and actuated dynamics on the neural manifold
→ a method to learn control signals
→ a dLDS model that is much faster than the original algorithm

Future Work?

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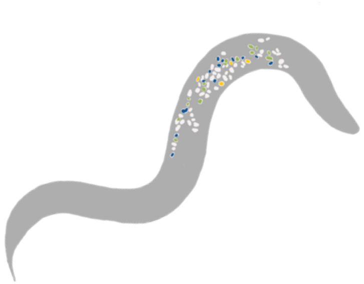

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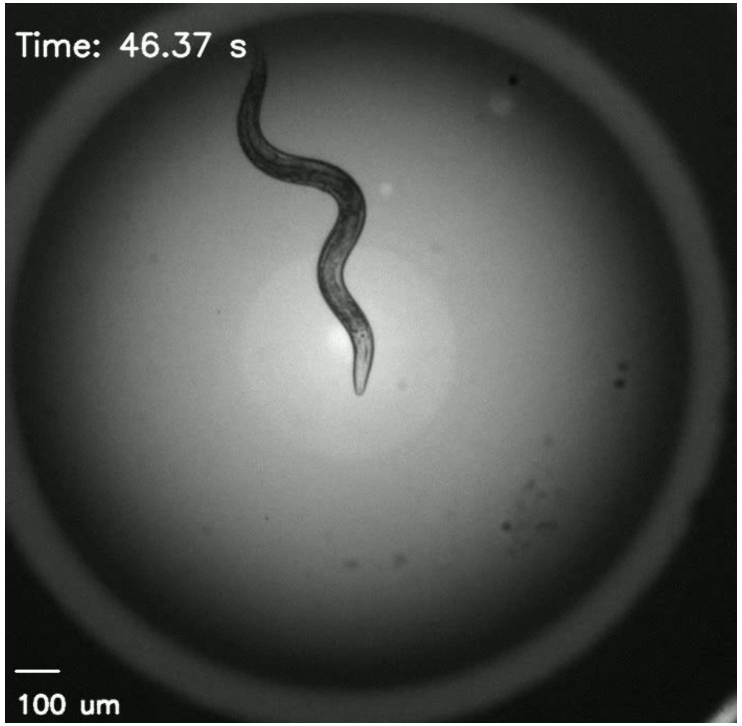
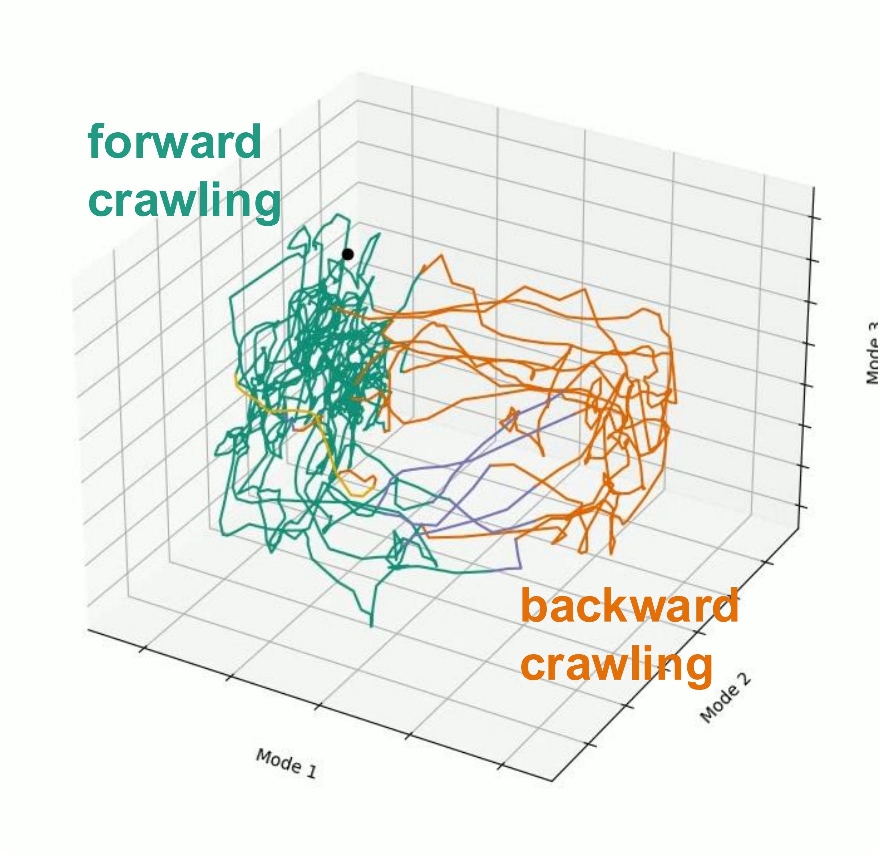
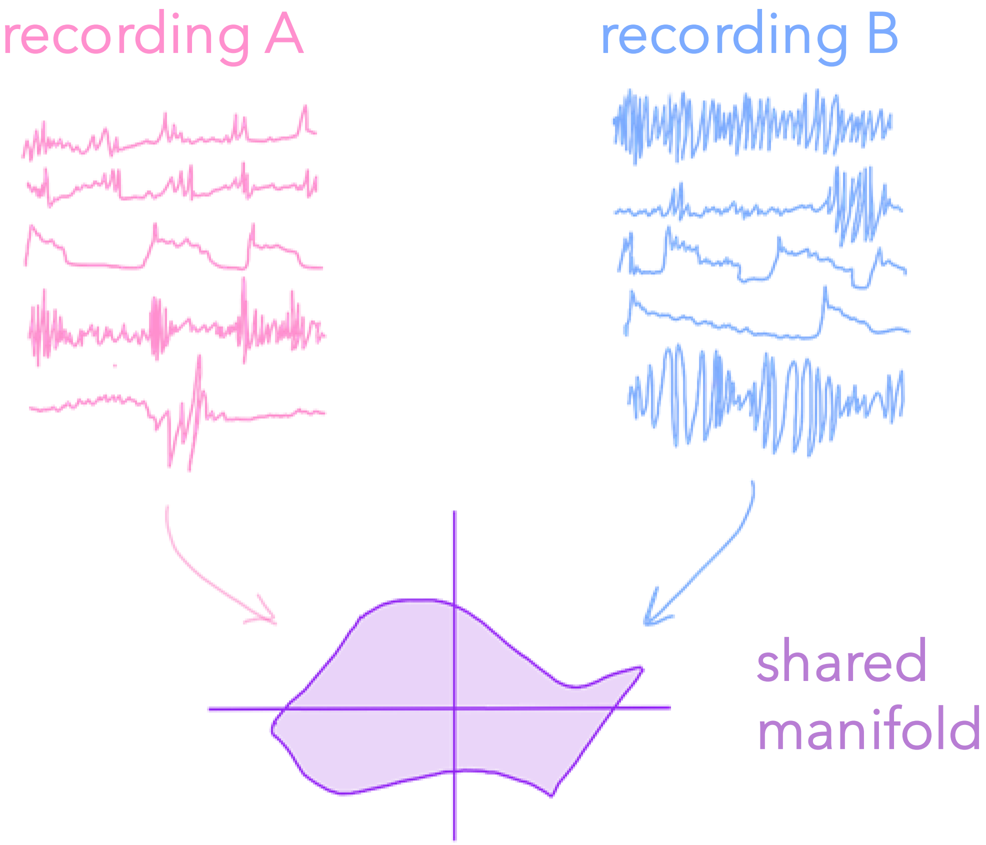
# An *elegant* organism to study whole brain dynamics



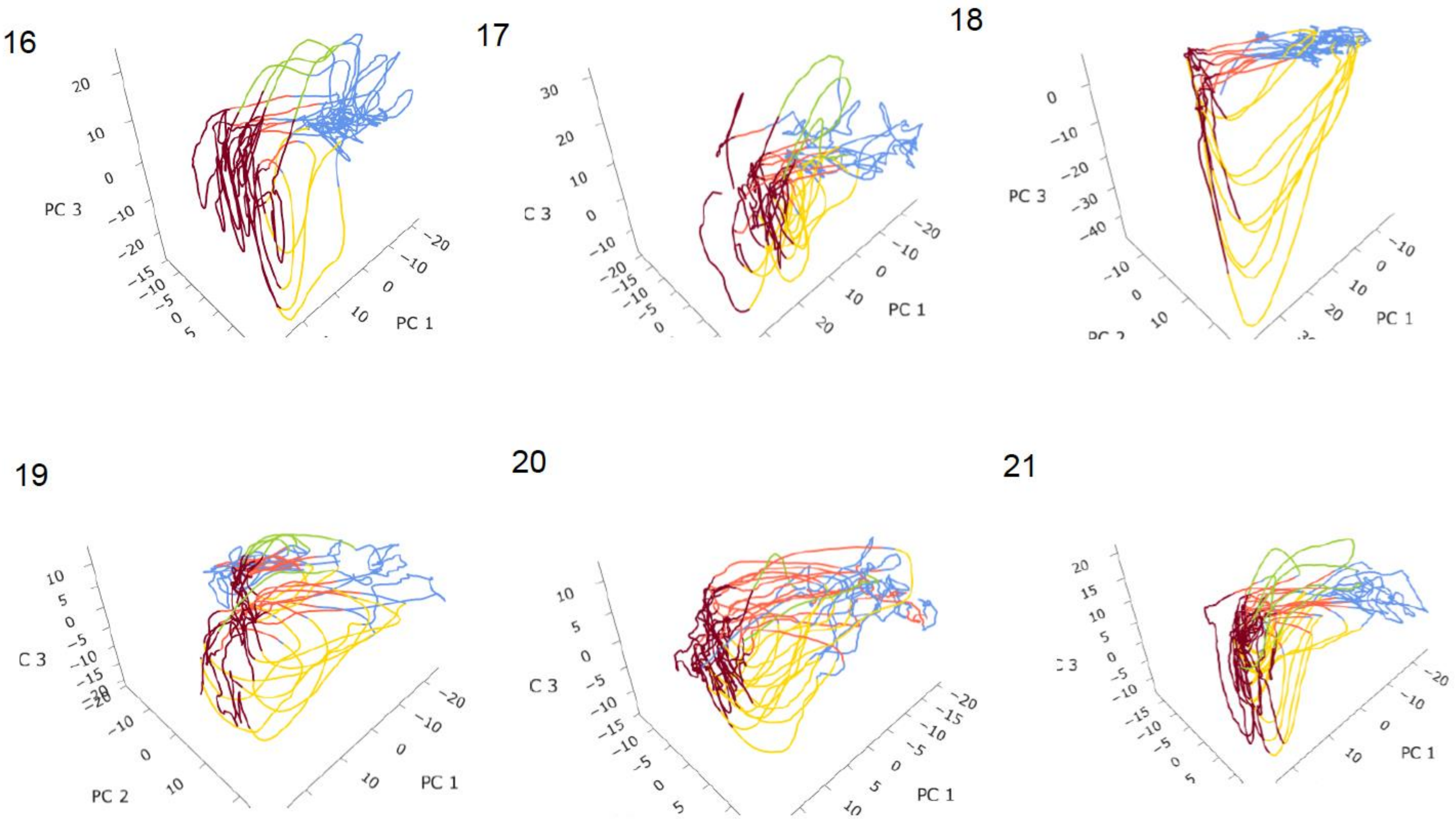



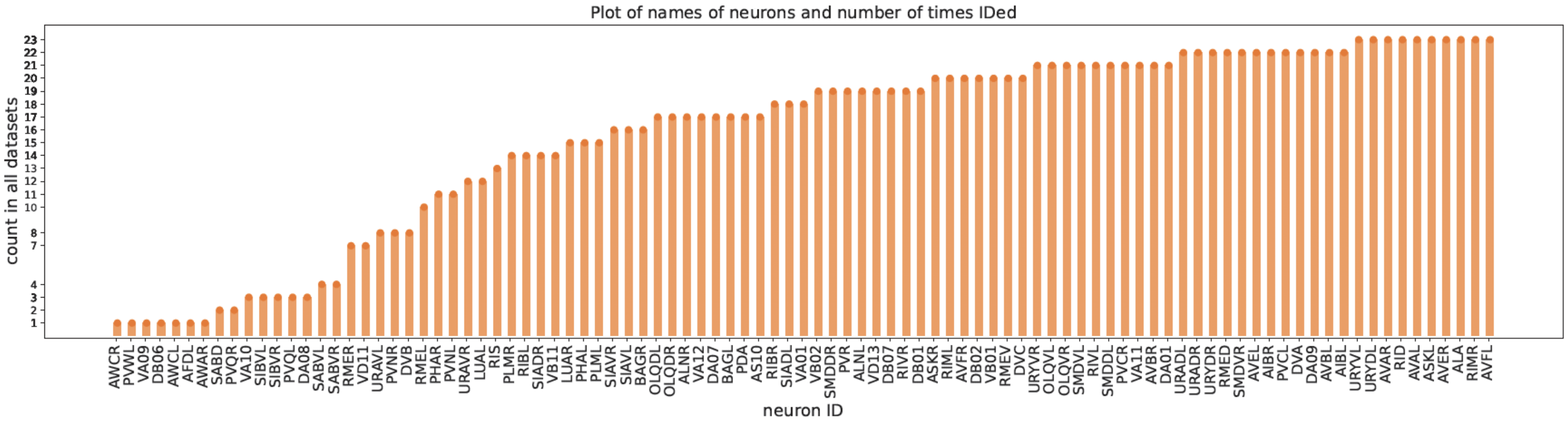

*Video and Visualization Source: Charles Fieseler (UniVie)*



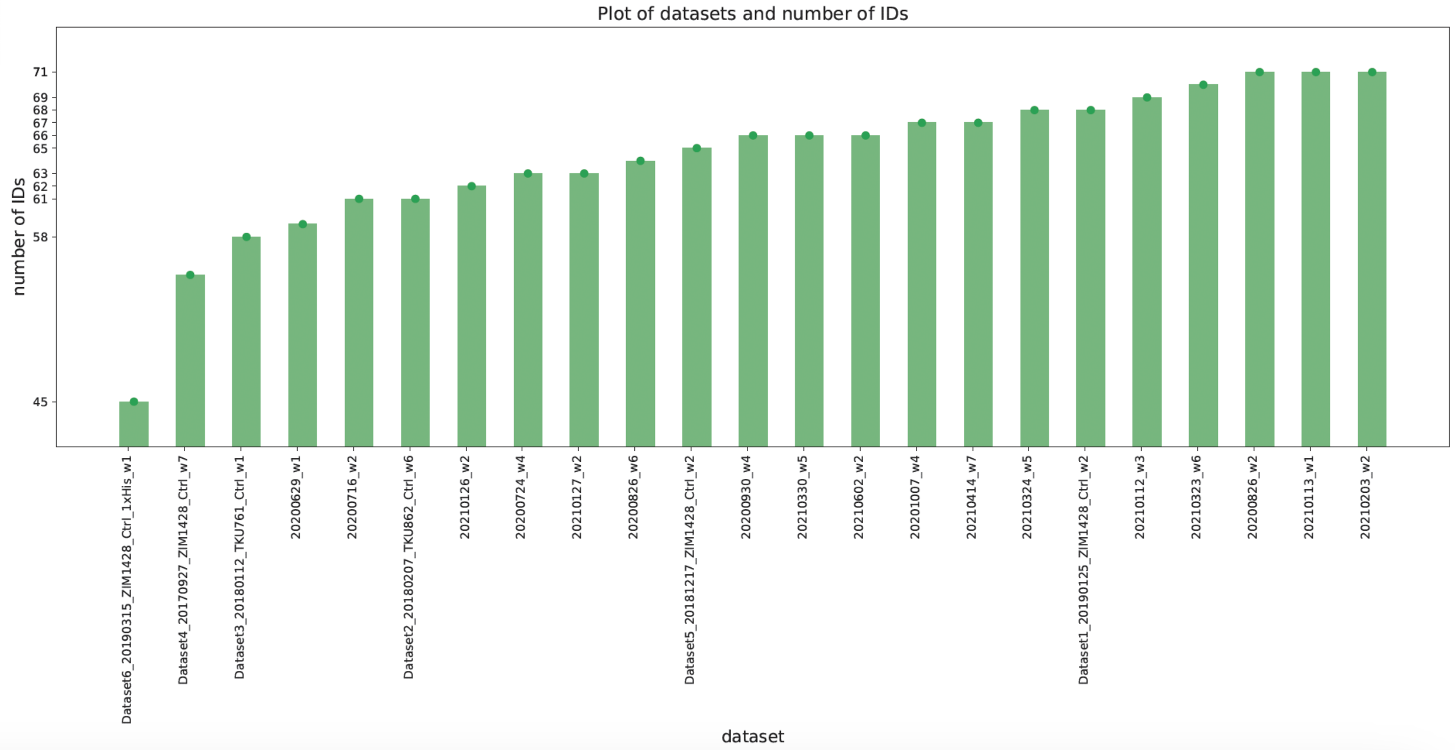

Given the inconsistencies across recordings, what preprocessing steps are required to align neural activity data of individual C. elegans in order to obtain a canonical manifold?

# Individual data sets projected to shared PC space



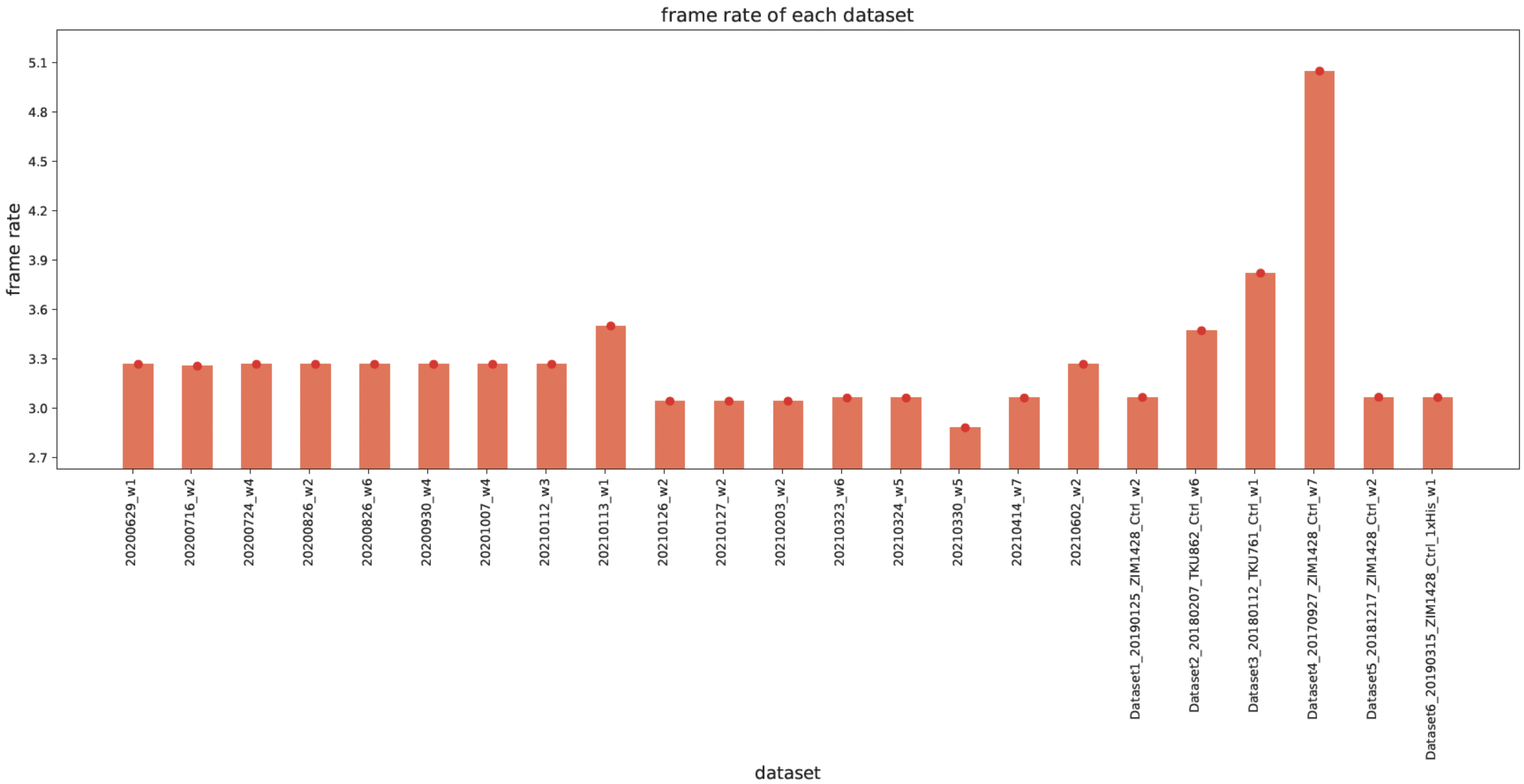



**Number of datasets in which each neuron is identified**

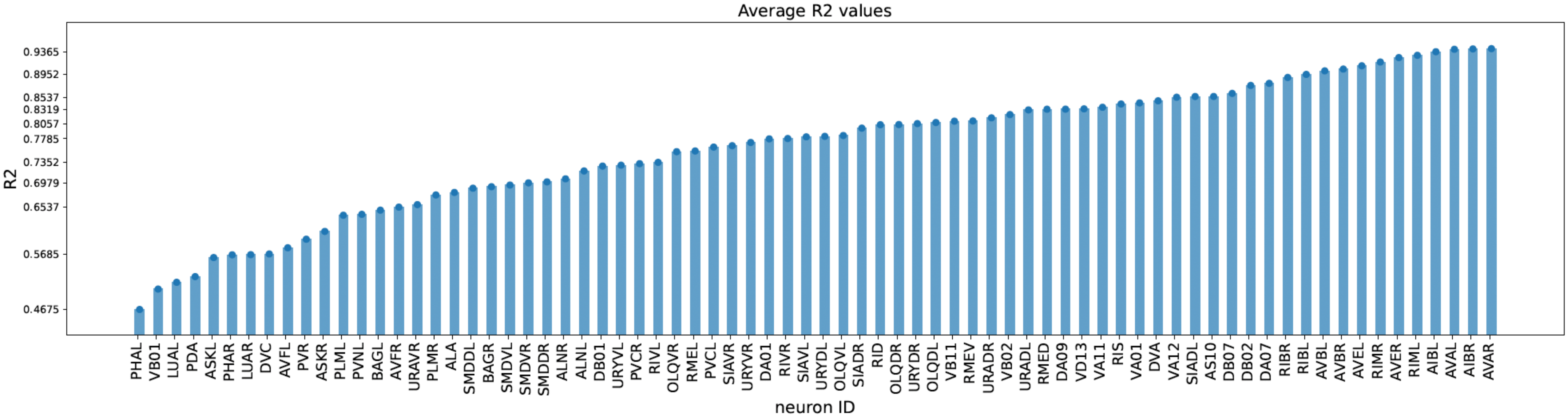



**Number of neurons that have been identified in each dataset**

# The frame rate varies across recordings

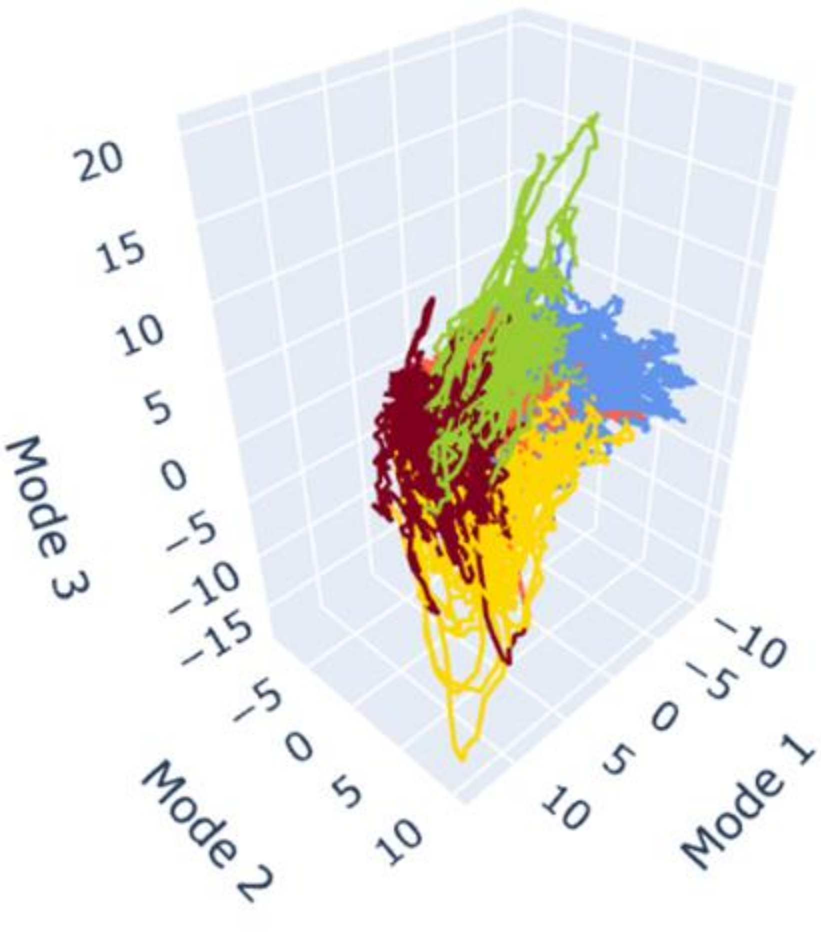


# PLSR determines a lack of uniqueness in most neurons (PPCA check)

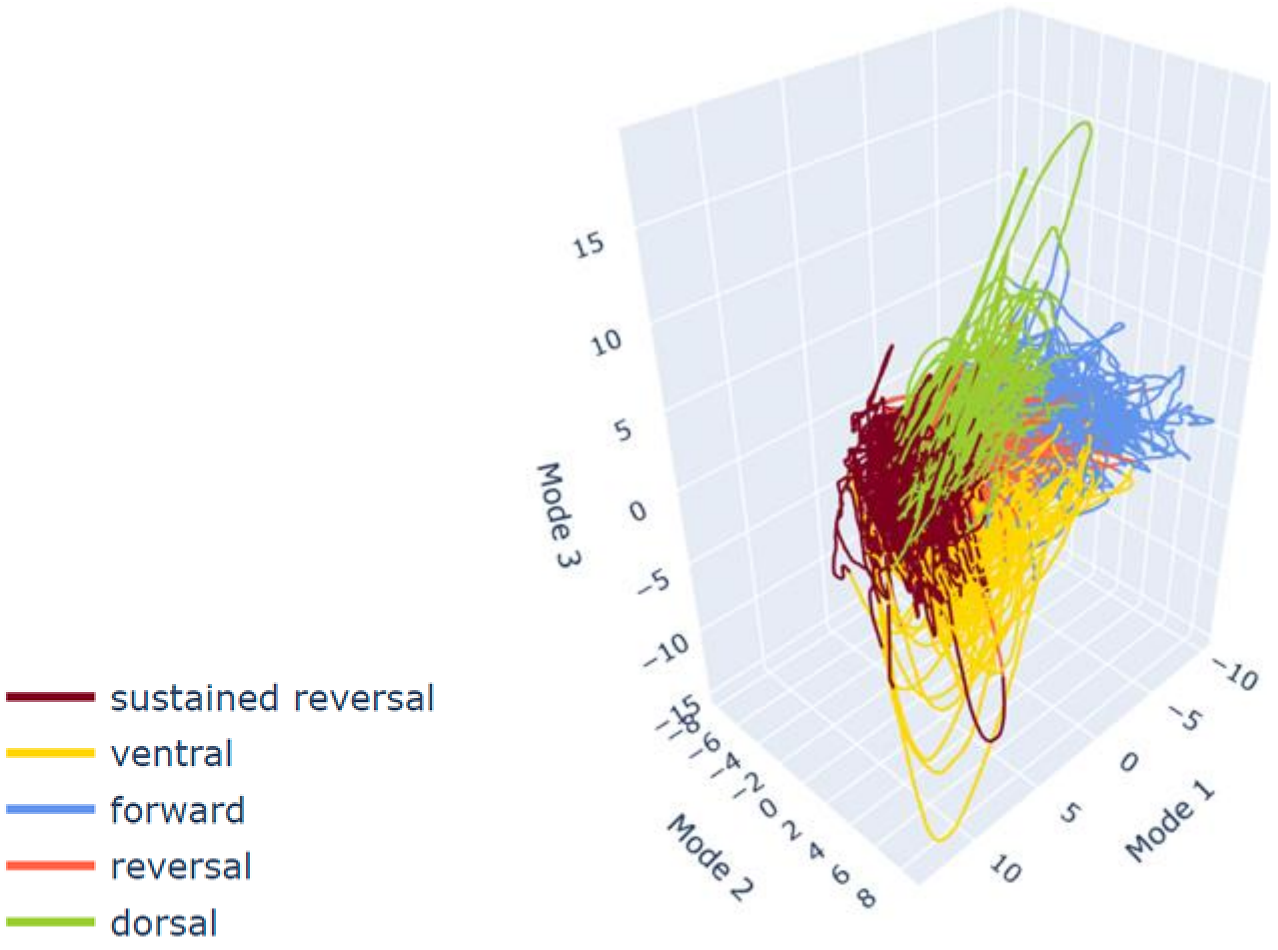


# Preprocessing steps that worked

WITHOUT TIME DELAY EMBEDDING

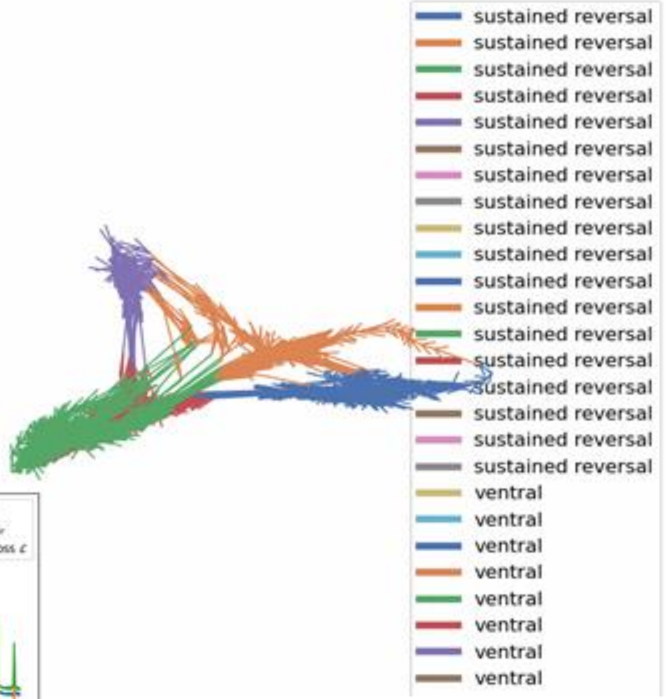


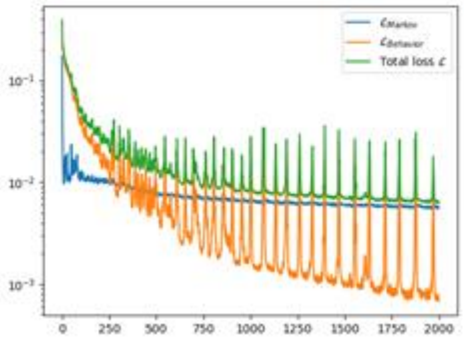

WITH TIME DELAY EMBEDDING



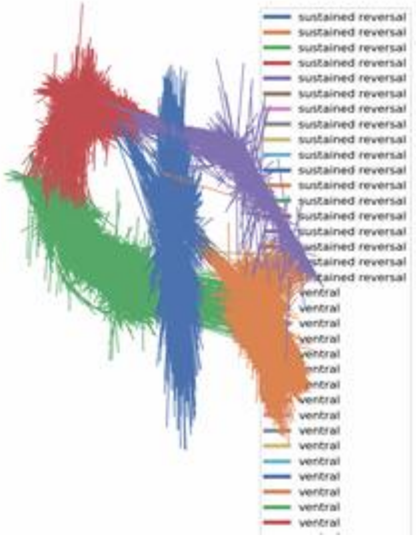
# BunDLe-Net

dataset 1

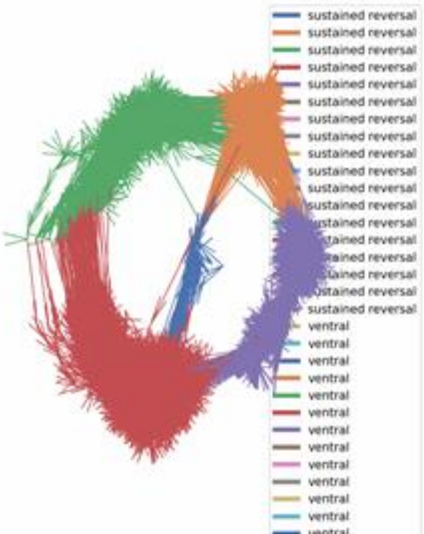



datasets up to 7



datasets up to 8



# CLUSTERING I

→ use k-means to cluster data points into 23 clusters and check the similarity between the predicted clusters and the true dataset clusters
→ evaluate with adjusted mutual information score*

$$AMI(U, V) = [MI(U, V) - E(MI(U, V))] / [avg(H(U), H(V)) - E(MI(U, V))]$$

| AMI | High-Dim (Raw) | Low-Dim (Raw) | Neural Manifold |
|---|---|---|---|
| All states | 0.332 | 0.277 | 0.219 |

after applying the preprocessing steps there is a huge decrease in similarity between the predicted clustering and the dataset membership

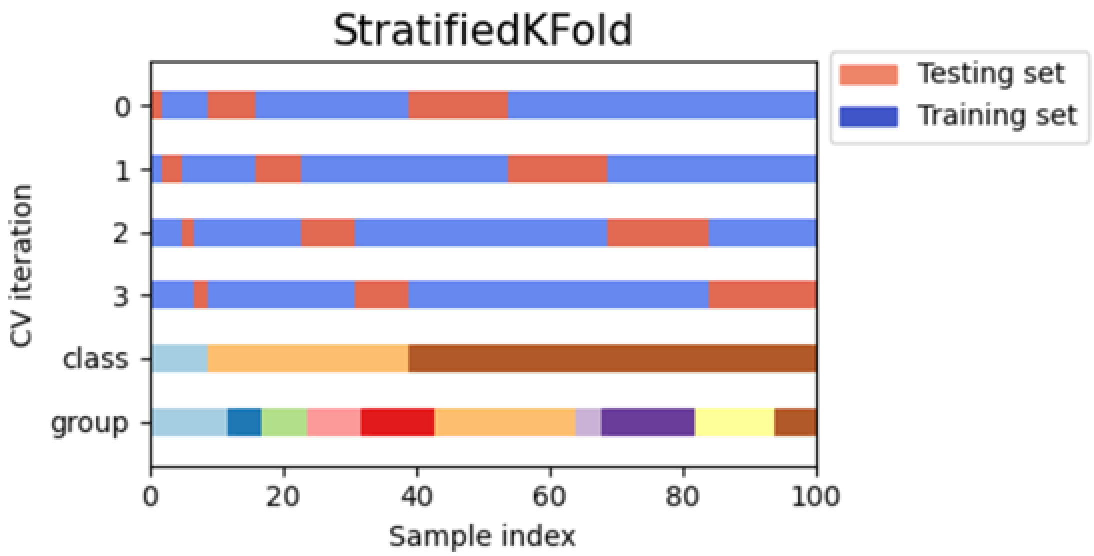
*where 1.0 == identical

# CLASSIFICATION I

→ use **simple linear model** to classify time points

→ dataset membership. If model performs poorly then this might indicate that there is not much difference between the datasets

→ **train-test split** based on **StratifiedKFold**



# CLASSIFICATION I

→ use SVC = Support Vector Machine (Classifier)
→ dataset membership

| Metric | High-Dim (Raw) | High-Dim | Low-Dim (Raw) | Neural Manifold |
|---|---|---|---|---|
| accuracy | 0.872 | 0.481 | 0.192 | 0.058 |
| precision | 0.905 | 0.522 | 0.181 | 0.061 |
| recall | 0.872 | 0.480 | 0.192 | 0.058 |
| f1 | 0.869 | 0.475 | 0.166 | 0.058 |

after preprocessing, all metric scores decrease dramatically, meaning that observations from different recordings are not distinguishable = variability might not be explained by dataset

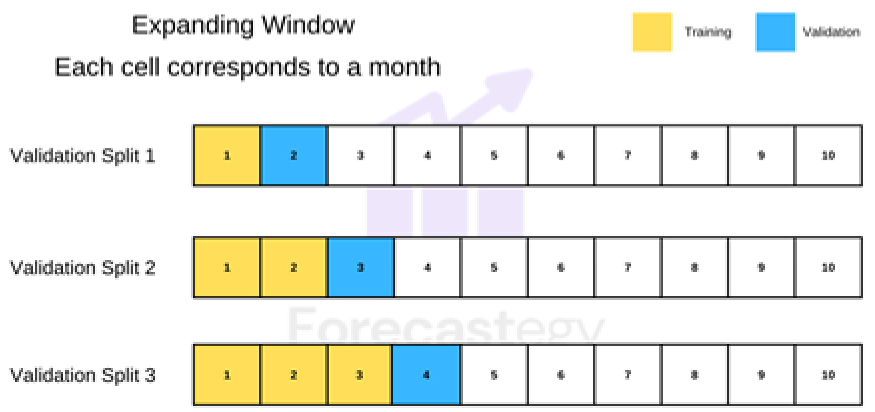
# CLASSIFICATION II

→ use **simple linear model** to classify time points

→ dataset membership. If model performs poorly then this might indicate that there is not much difference between the datasets

→ behaviour state. If model performs poorly then this might indicate that there is no clear separation between the states

→ **train-test split** based on '**expanding window cross-validation**'




`sklearn.model_selection.`TimeSeriesSplit

**image from forecastegy*

# CLASSIFICATION II

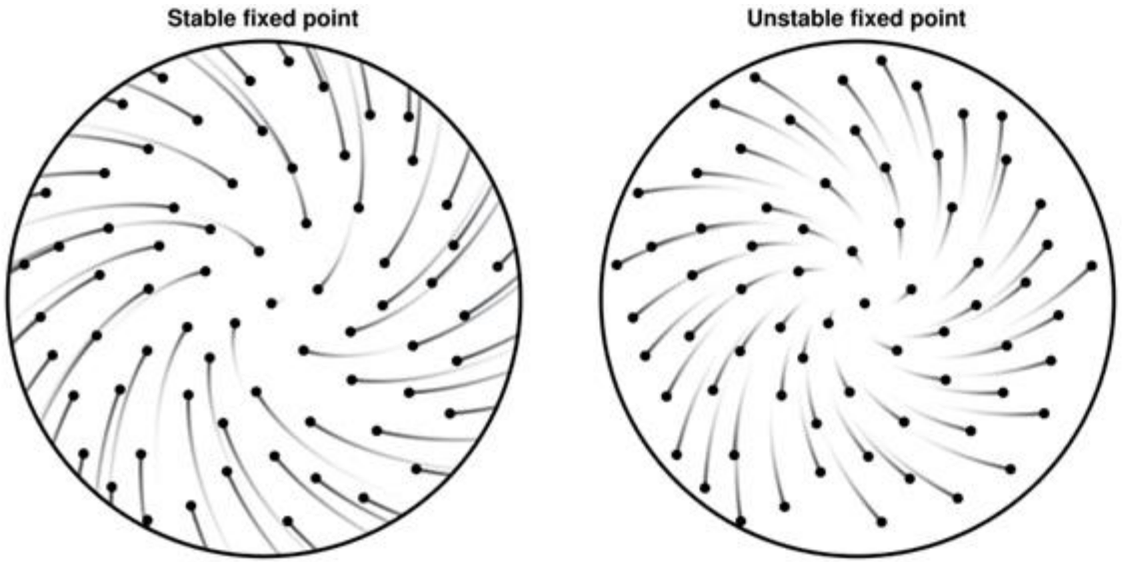
→ use SVC = Support Vector Machine (Classifier)
→ behaviour states

| Metric | High-Dim (Raw) | High-Dim | Low-Dim (Raw) | Neural Manifold |
|---|---|---|---|---|
| Accuracy | 0.732 | 0.901 | 0.809 | 0.760 |
| Precision | 0.777 | 0.901 | 0.78 | 0.799 |
| Recall | 0.732 | 0.901 | 0.809 | 0.760 |
| F1 | 0.723 | 0.899 | 0.780 | 0.759 |

# Synthetic Data to reflect switches between linear dynamical systems

$$x_{t+1} = \sum \begin{matrix} 0 \times A_1 x_t \\ 1 \times A_2 x_t \\ \vdots \\ 0 \times A_n x_t \end{matrix}$$

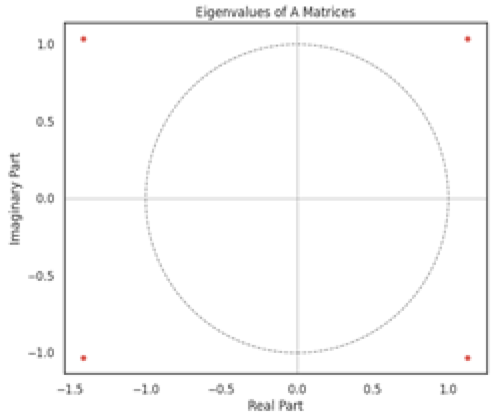
choice of eigenvalues determines stability of the system

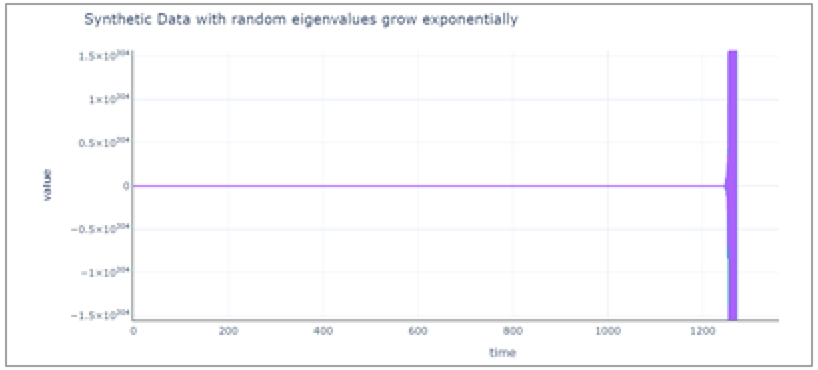



animation by Jacopo Bertolotti

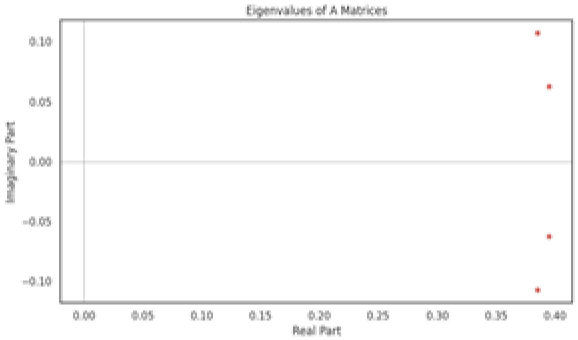
# Synthetic Data to reflect switches between linear dynamical systems

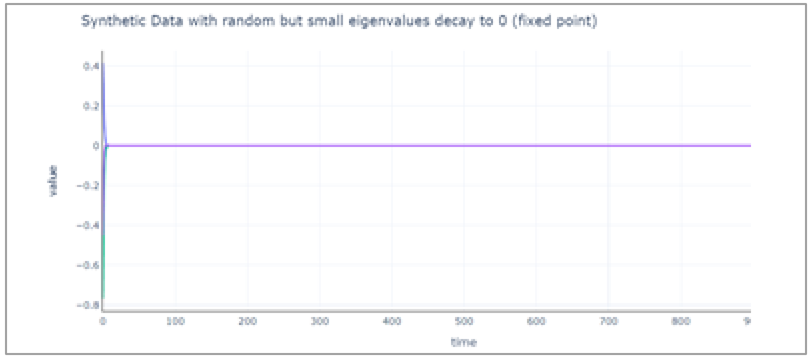
**λ > 1**



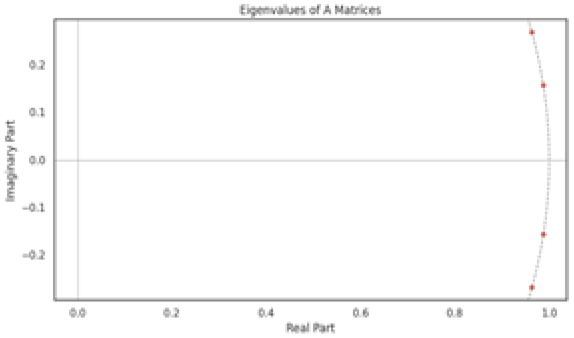



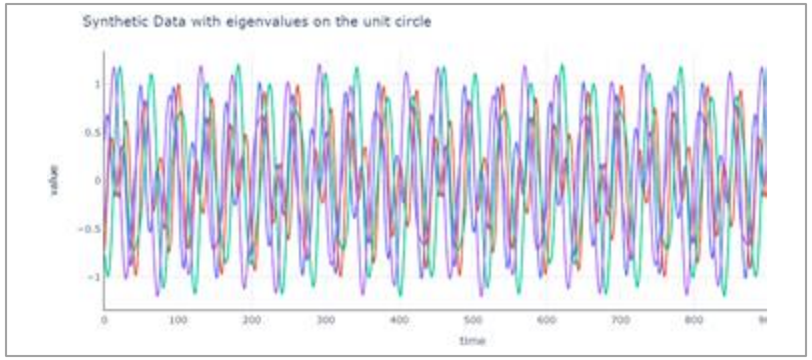

**λ < 1**



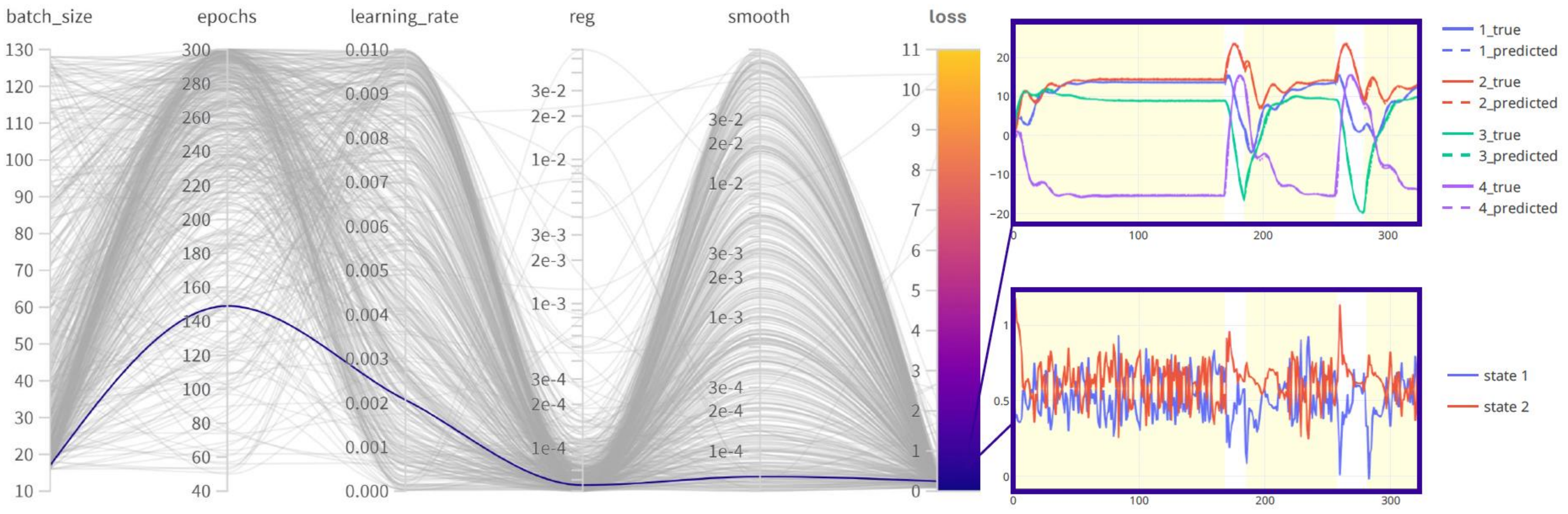




**λ = 1**

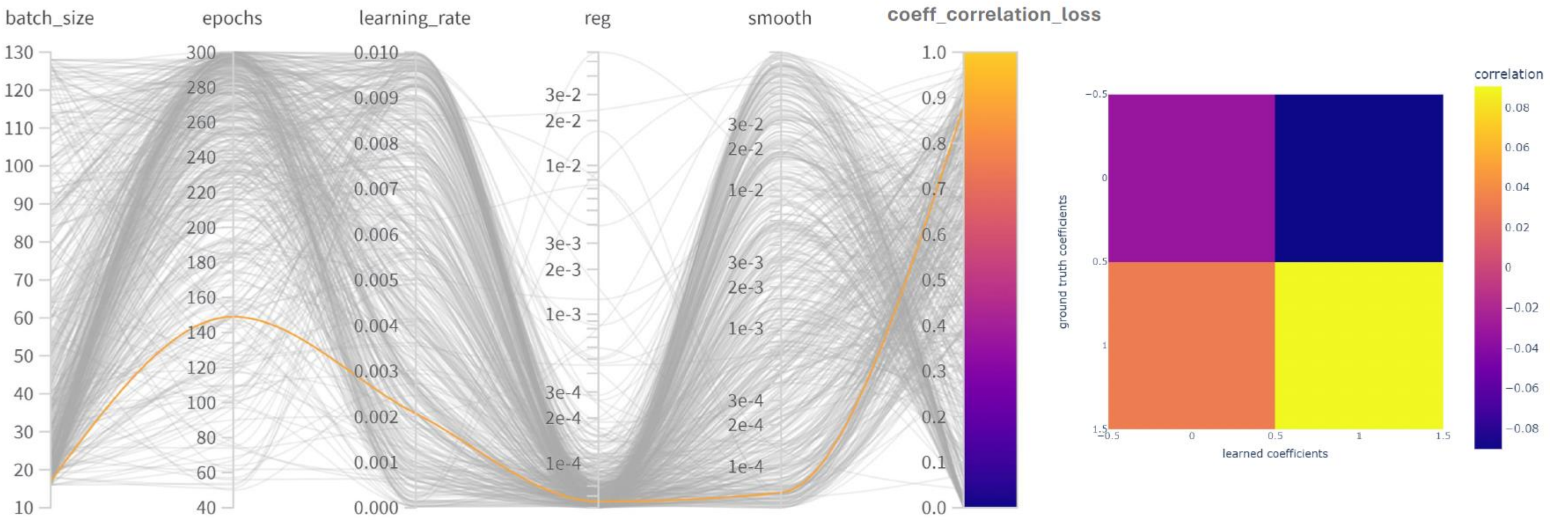


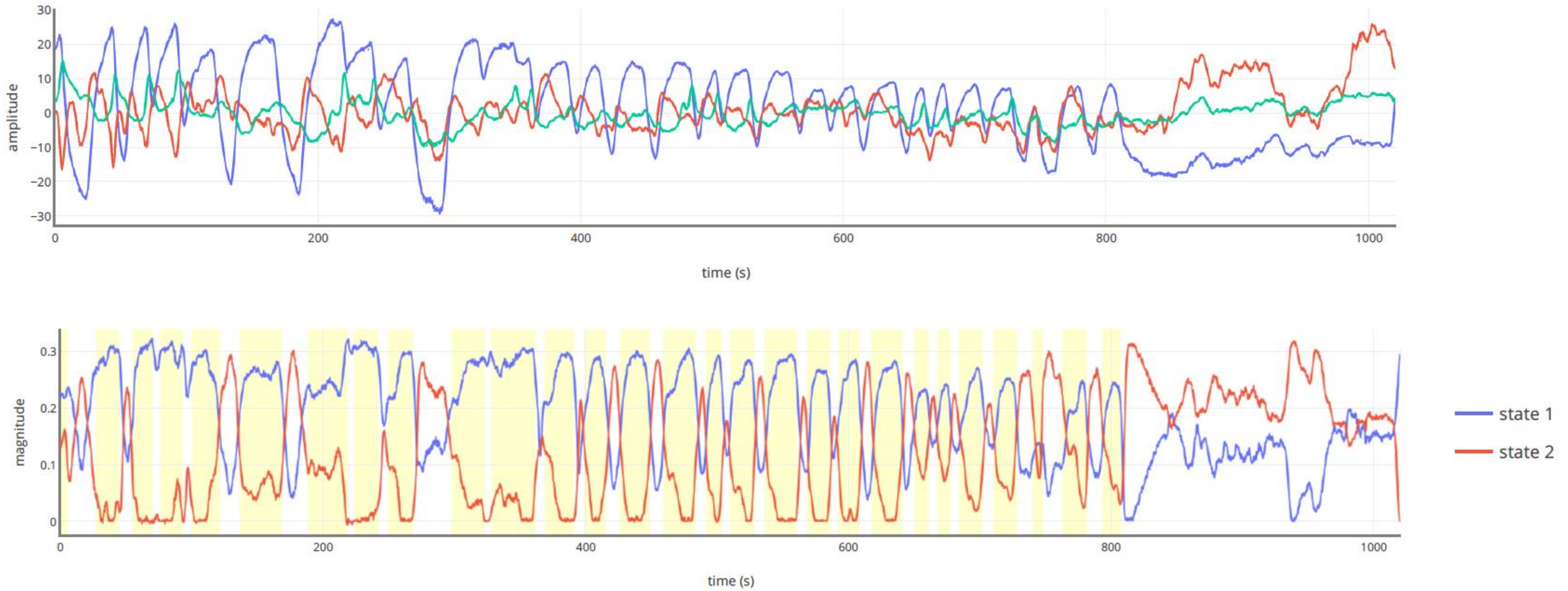
# A low dLDS loss does not imply interpretable coefficients..




## and indicates the need for an additional evaluation metric

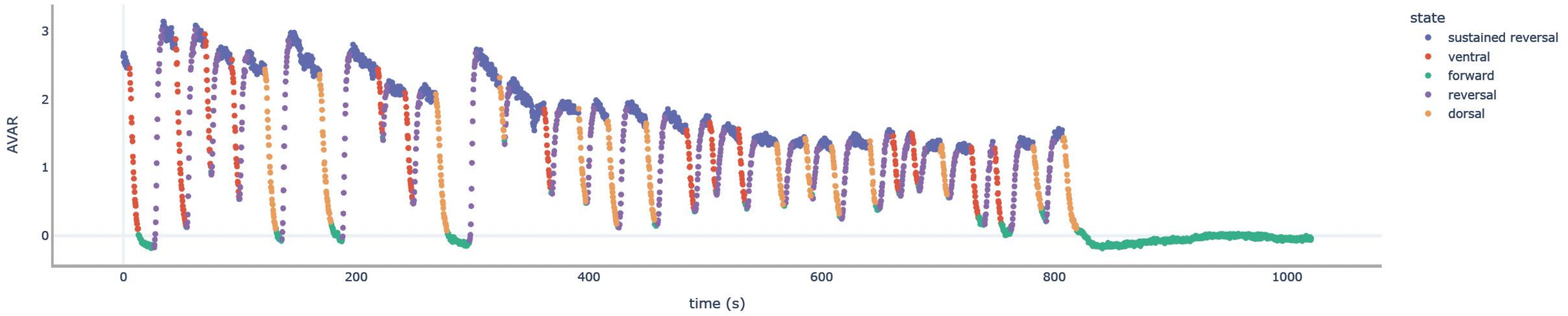


# Neural Manifold latent states correspond to behavior states




**dLDS applied to a single recording projected to the Canonical Neural Manifold.** The yellow highlights indicate where the worm is in a reversal state, as opposed to the forward state, which remains unhighlighted.

# Intrinsic vs. actuated dynamics in C. elegans




Activity of reversal driver AVA and correlated neurons show ‘pirouettes’. What is from a behaviour perspective a period of frequent turns might be the system failing to stabilize.

This could be explained by a computational model that can infer actuated dynamics.

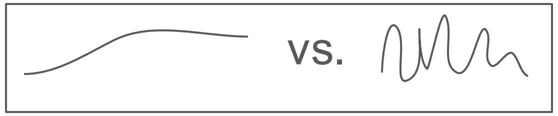
# Reformulating dLDS as a feed-forward Neural Network

## Why?

- Additional components like the controls can be integrated more easily
- Lower runtime for equal or better performance
- State of the Art
- MLOps can be leveraged for monitoring computational experiments

# What can go wrong?

- **Bad Hyperparameters**
  - # of epochs
  - batch size
  - learning rate
- **Bad Regularization/Loss Functions**
  - smoothness over time-varying coefficients
  - mean squared error




$$\mathrm{MSE} = \overset{\text{Mean}}{\boxed{\frac{1}{n}\sum_{i=1}^{n}}}\,(\overset{\text{Error}}{\boxed{Y_i - \hat{Y}_i}})^{\overset{\text{Squared}}{\boxed{2}}}$$

$$\widehat{\boldsymbol{x}}_t, \widehat{\boldsymbol{c}}_t = \arg\min_{\boldsymbol{x}_t, \boldsymbol{c}_t} \left[ \|\boldsymbol{y}_t - \boldsymbol{D}\boldsymbol{x}_t\|_2^2 + \lambda_0 \left\|\boldsymbol{x}_t - \widetilde{\boldsymbol{F}}_t \boldsymbol{c}_t\right\|_2^2 + \lambda_1 \|\boldsymbol{x}_t\|_1 + \lambda_2 \|\boldsymbol{c}_t\|_1 + \lambda_3 \|\boldsymbol{c}_t - \widehat{\boldsymbol{c}}_{t-1}\|_2^2 \right]$$

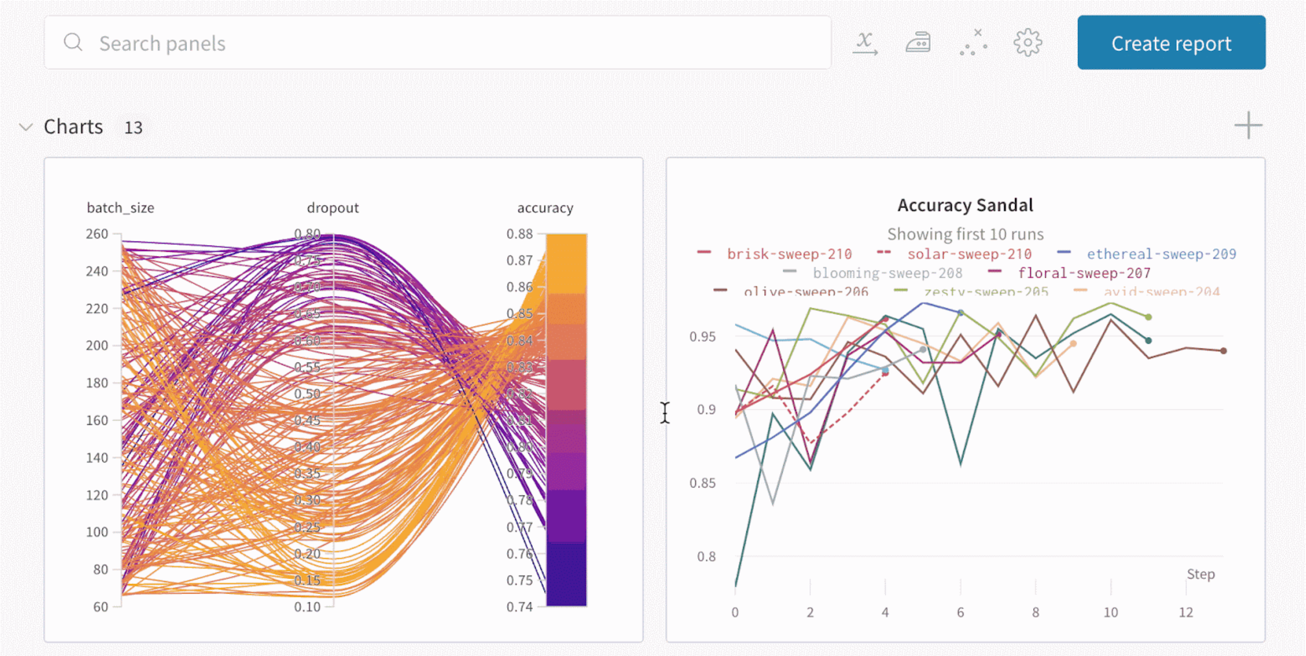
*formula from https://suboptimal.wiki/explanation/mse/*

# dLDS Experimental Conditions

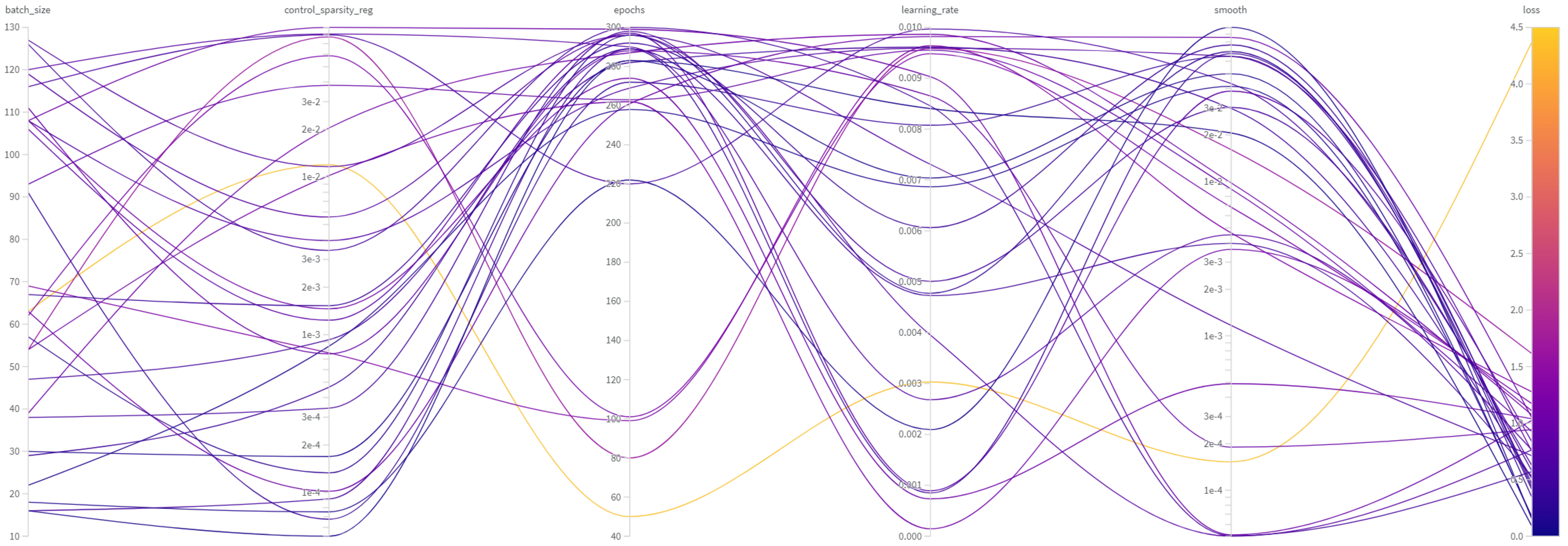
1. Ground Truth Initialization
2. True F Initialization
3. True c Initialization
4. Random Initialization

per condition we can run a sweep over hyperparameters with:

Weights & Biases

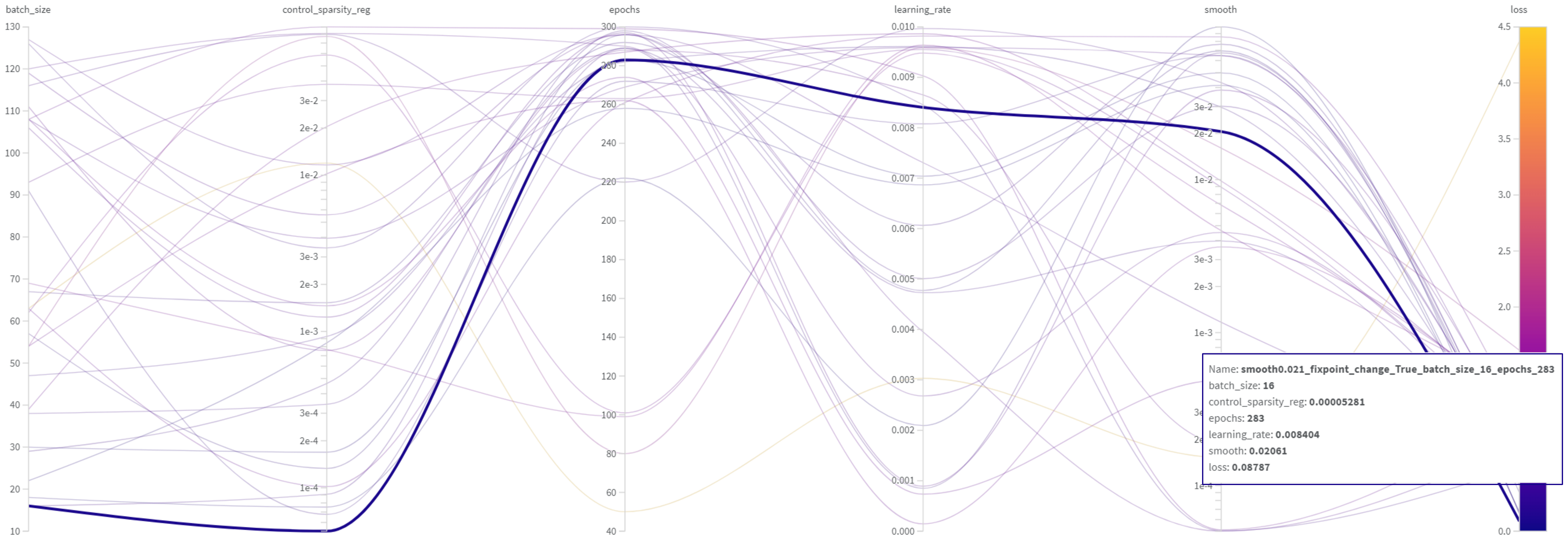


# dLDS Experimental Conditions - Example




Weights & Biases

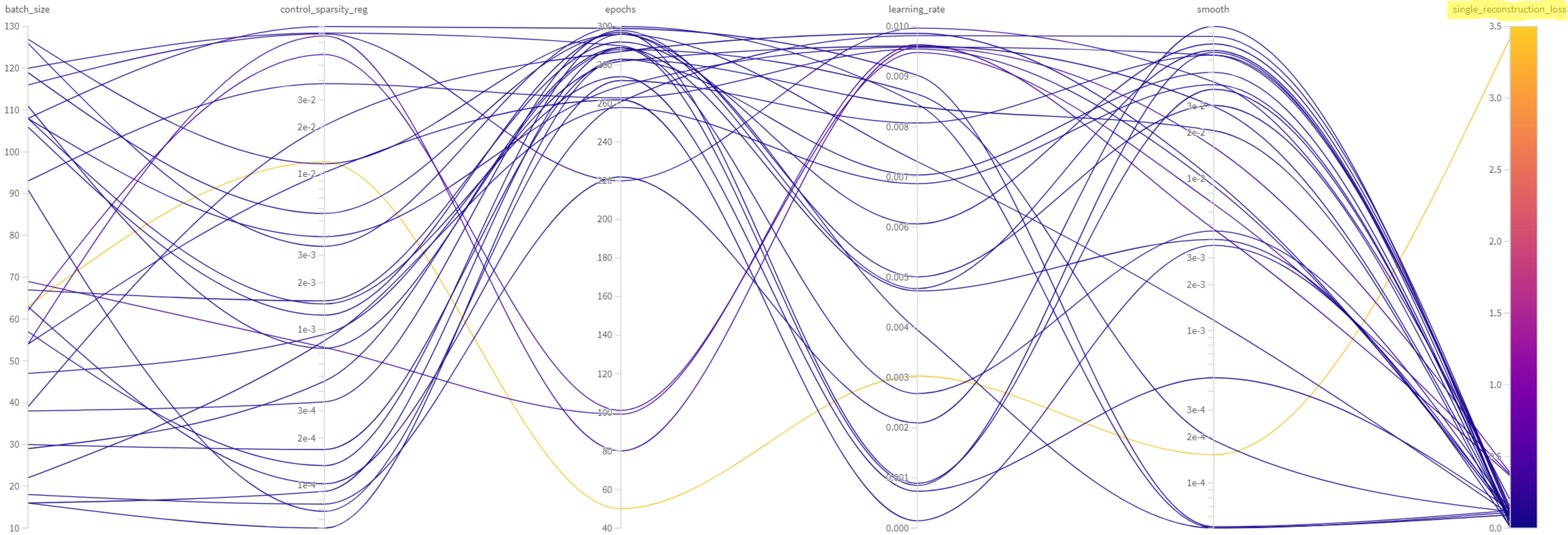
# dLDS Experimental Conditions - Example




Weights & Biases

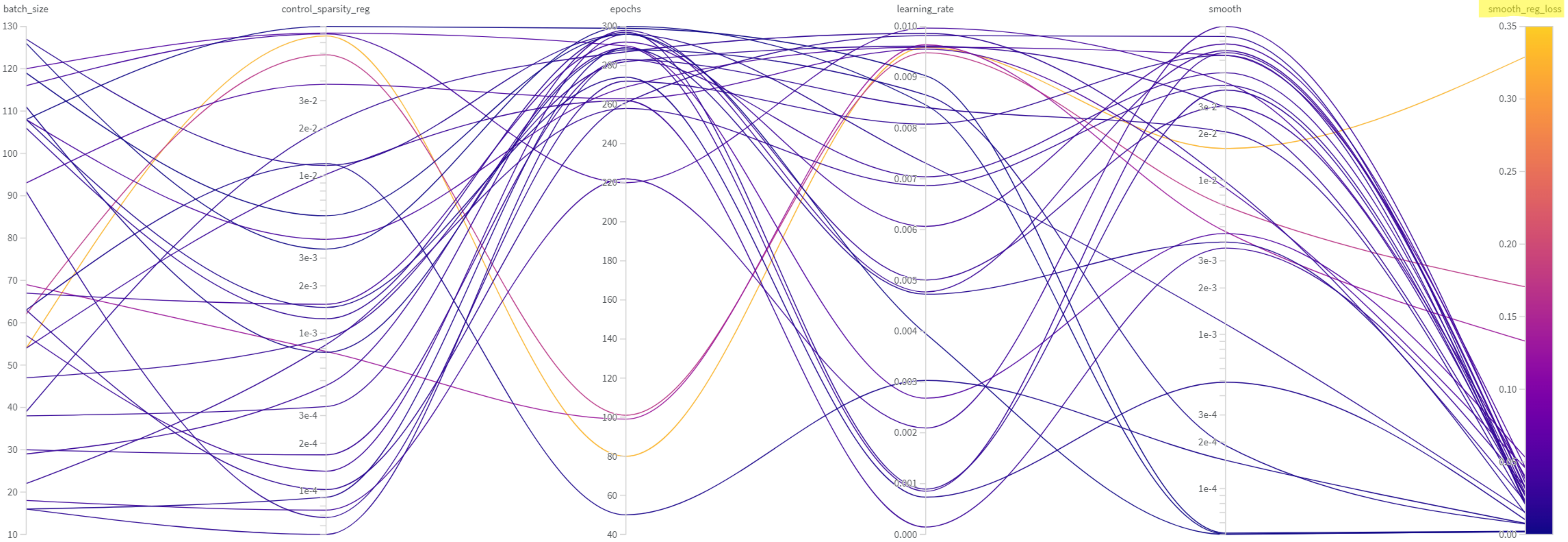
# dLDS Experimental Conditions - Example

$$\text{MSE} = \underbrace{\frac{1}{n}\sum_{i=1}^{n}}_{\text{Mean}}\underbrace{(Y_i - \hat{Y}_i)}_{\text{Error}}{}^{\overbrace{2}^{\text{Squared}}}$$



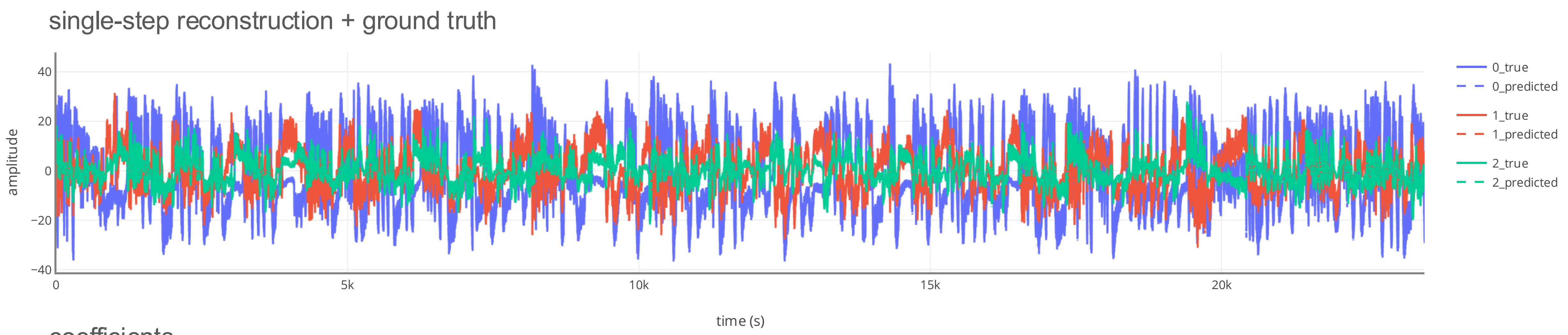

Weights & Biases

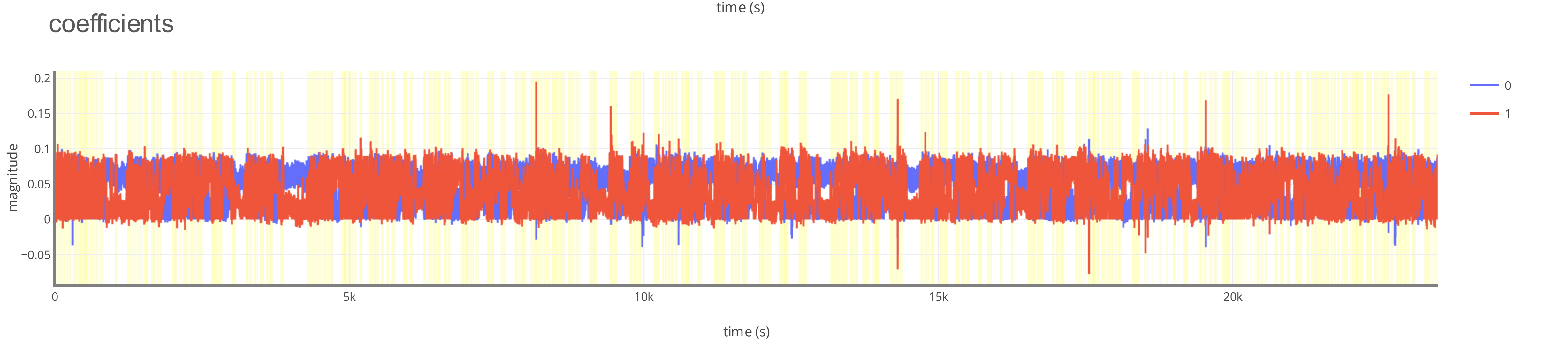
# dLDS Experimental Conditions - Example

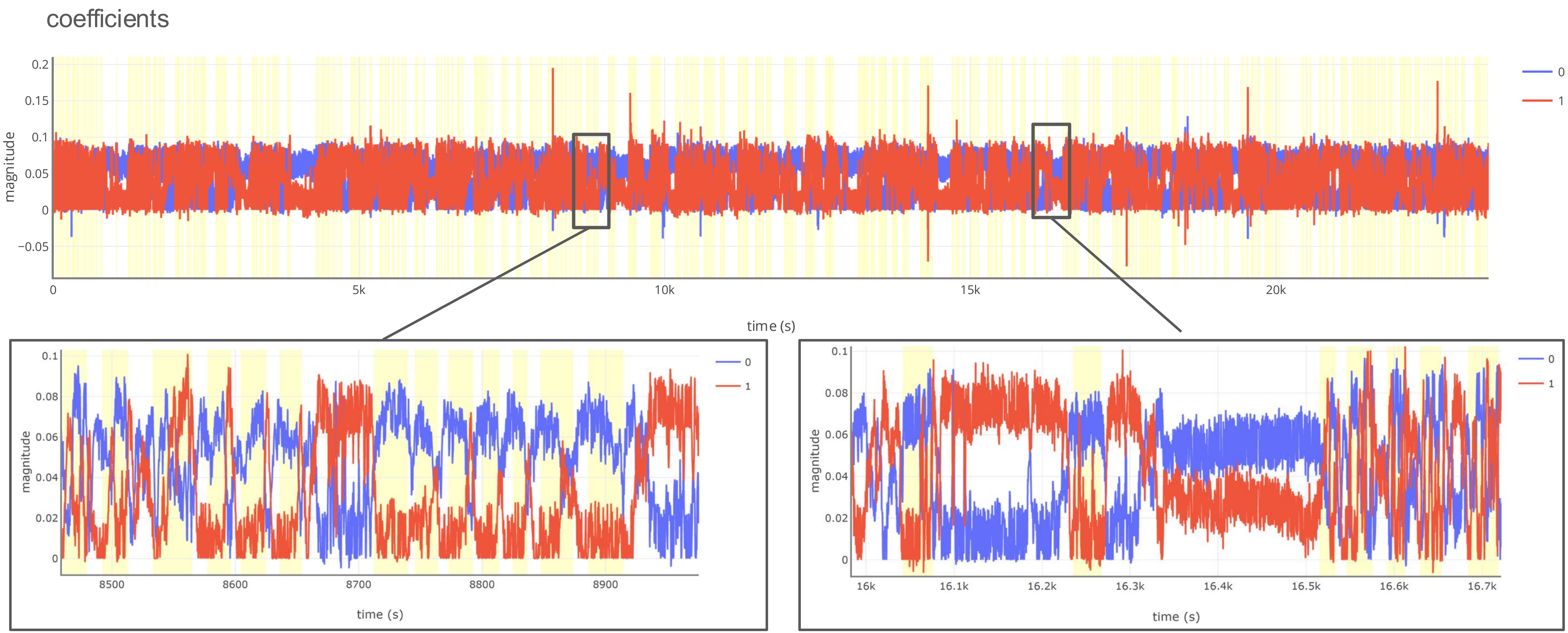

Weights & Biases

# dLDS applied to All Whole Brain Recordings projected to PC space



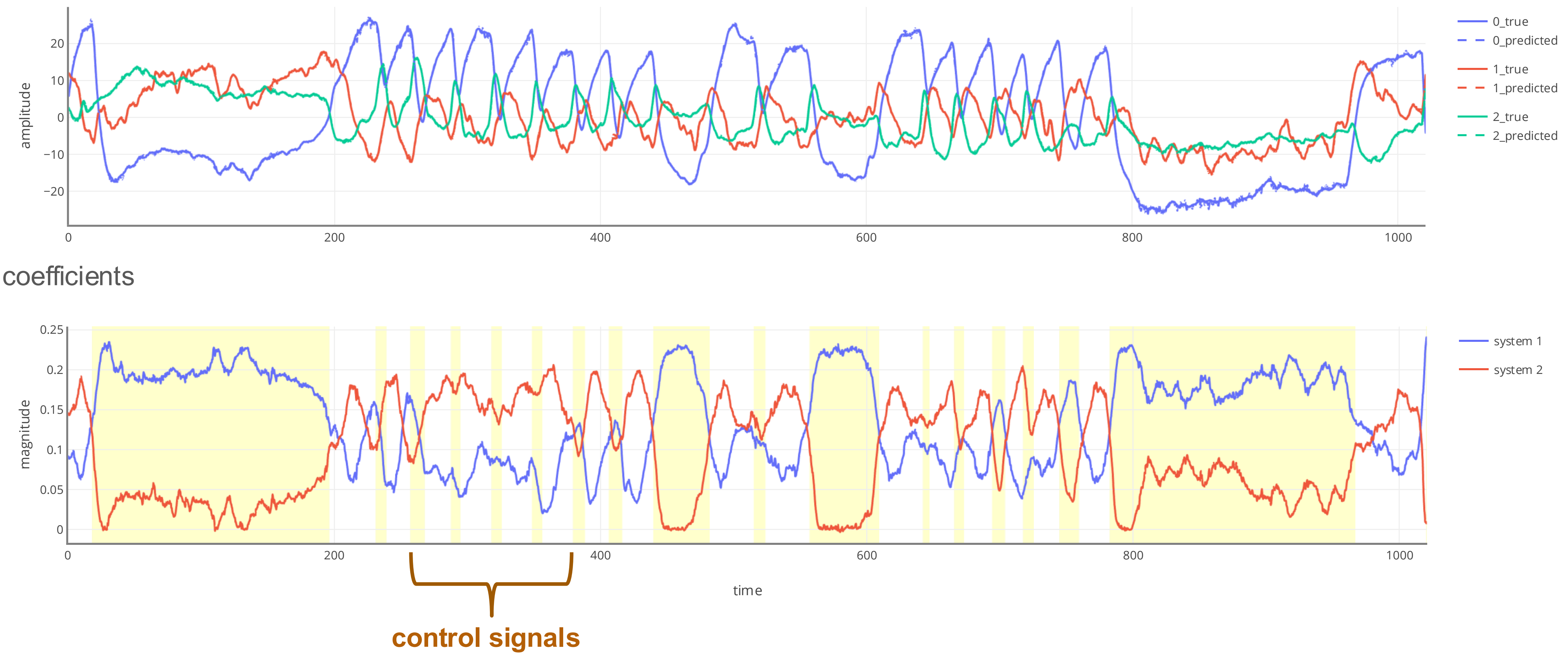



# dLDS applied to All Whole Brain Recordings projected to PC space



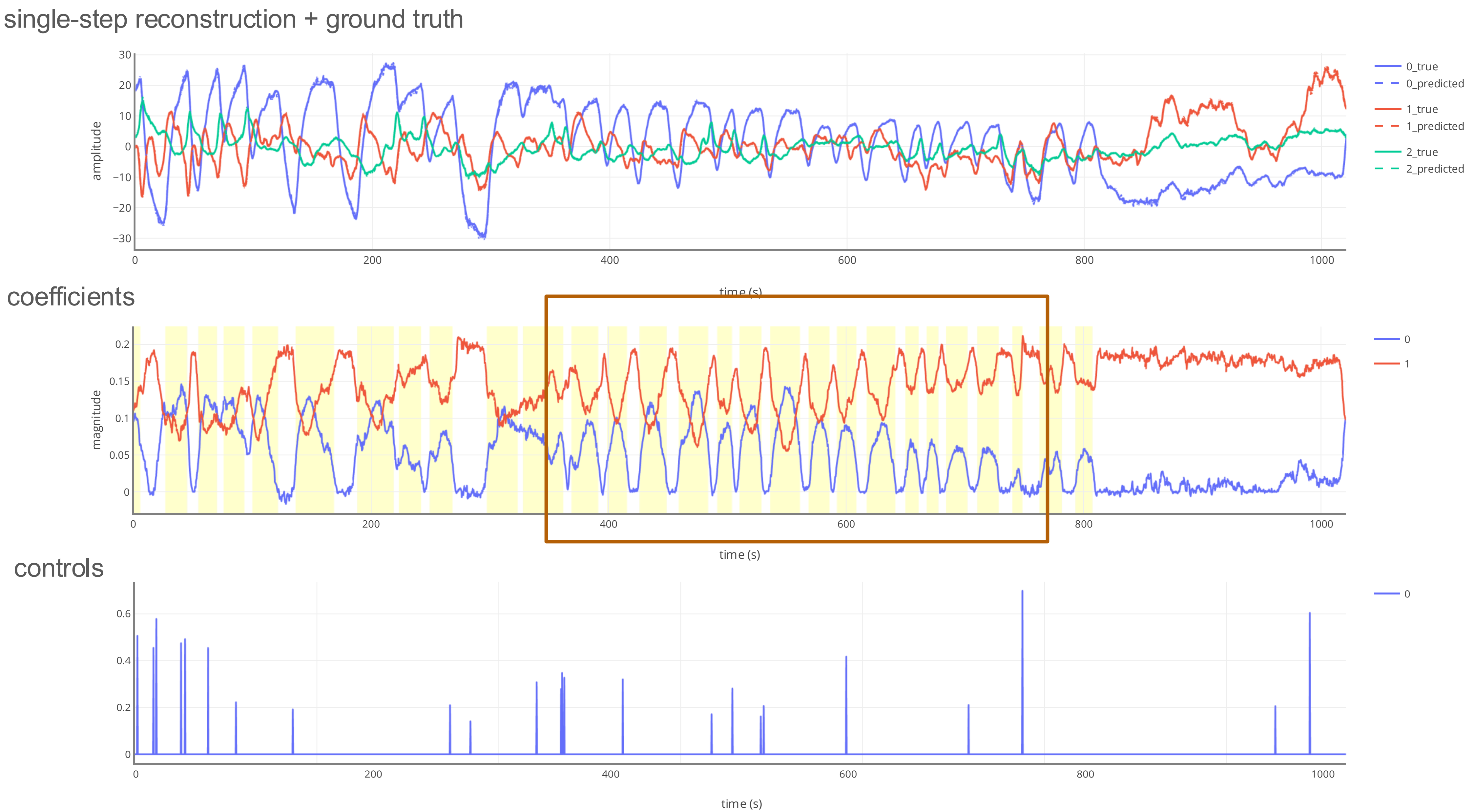
# dLDS applied to Single Whole Brain Recording projected to PC space

single-step reconstruction + ground truth




entire data fitted to PCA, DS2 projected onto that space

# cdLDS applied to Single Whole Brain Recording proj. to Neural Manifold



# Control Signal Initializations

## Potential Control Initialization: Short State Intervals