Inferring emerging structures and the embedding of content from neuronal firing data

Ho Fai Po , David Saad

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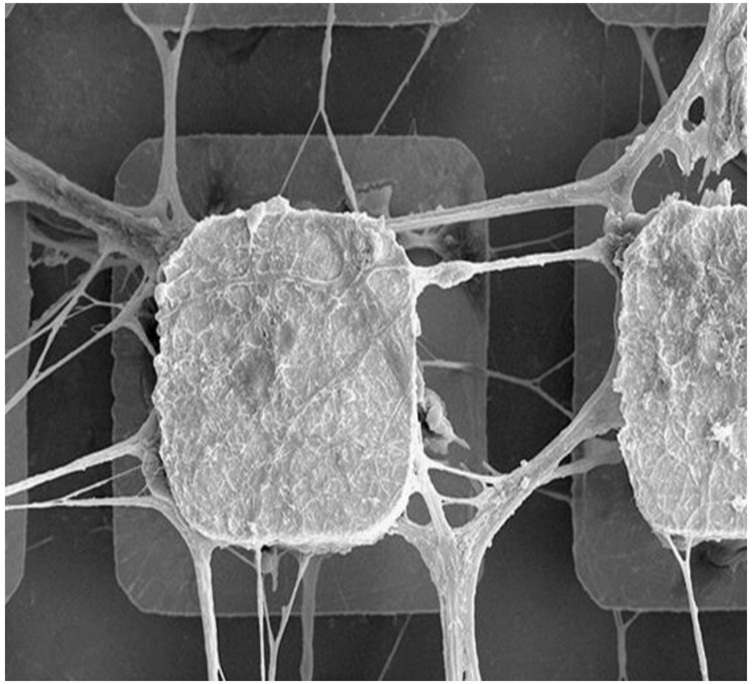
Outline

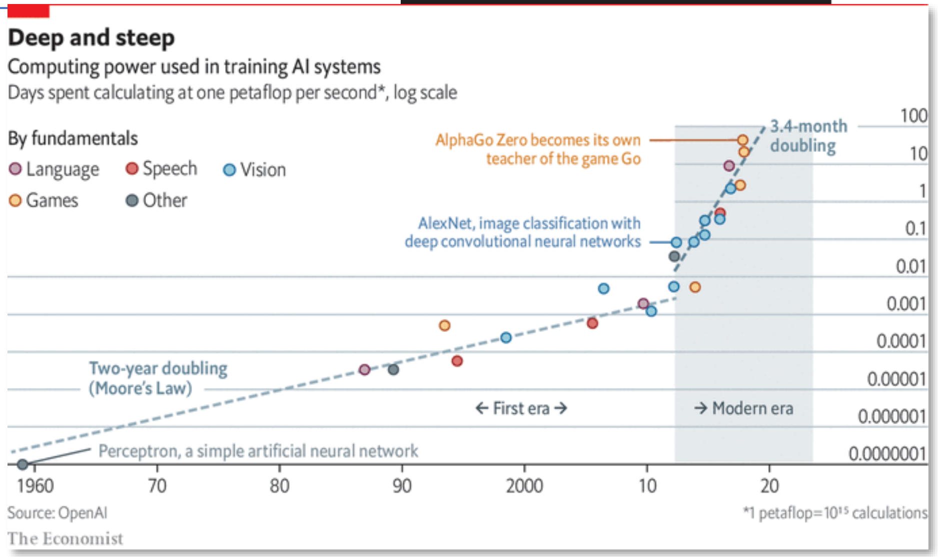
- Motivation for the NEU-CHiP project
- Challenges and focus of this work
- Neuronal network inferences
- Visual informatics of culture development
- Entropy as a measure of learning

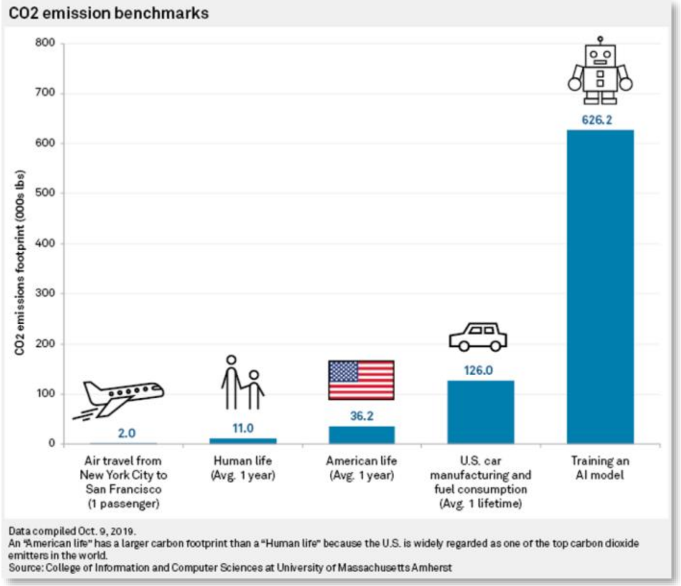


Inferring Structure of Cortical Neuronal Networks from Firing Data: A Statistical Physics Approach
Ho Fai Po, Akke Mats Houben, Anna-Christina Haeb, David Rhys Jenkins, Eric J. Hill, H. Rheinallt Parri, Jordi Soriano, David Saad
https://arxiv.org/abs/2402.18788

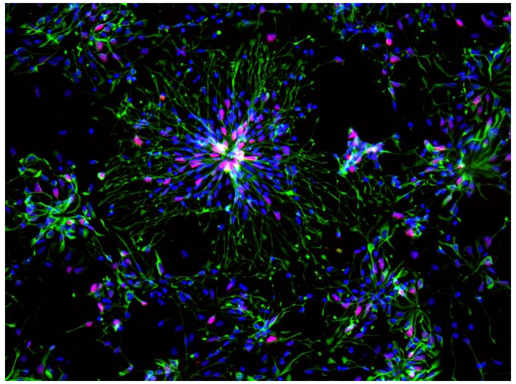
Background and Motivation

- Modern world increasingly relies on Machine Learning (ML) and Artificial intelligence (AI)
- Computational power used had doubled every 3.4 months since 2012 (200,000 times 2012-18)
- *Deep learning machines are not ideal*: unsustainable power consumption; inefficient training methods
- The brain works on about 20W, neurons learn without complex algorithms, are adaptive and robust against noise

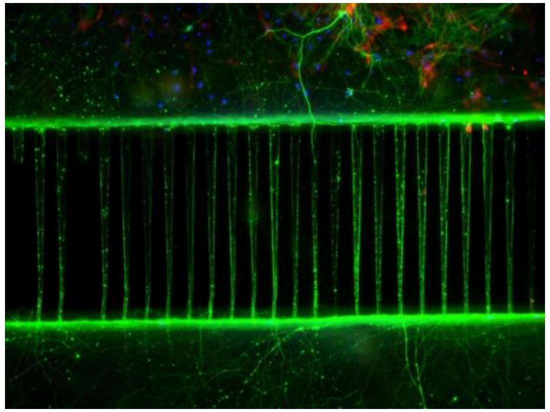




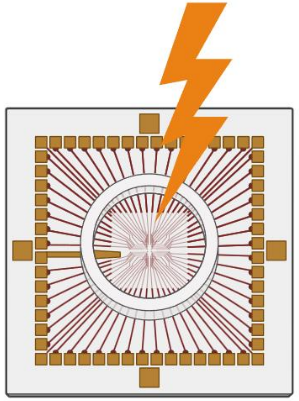
NEU-ChiP objectives



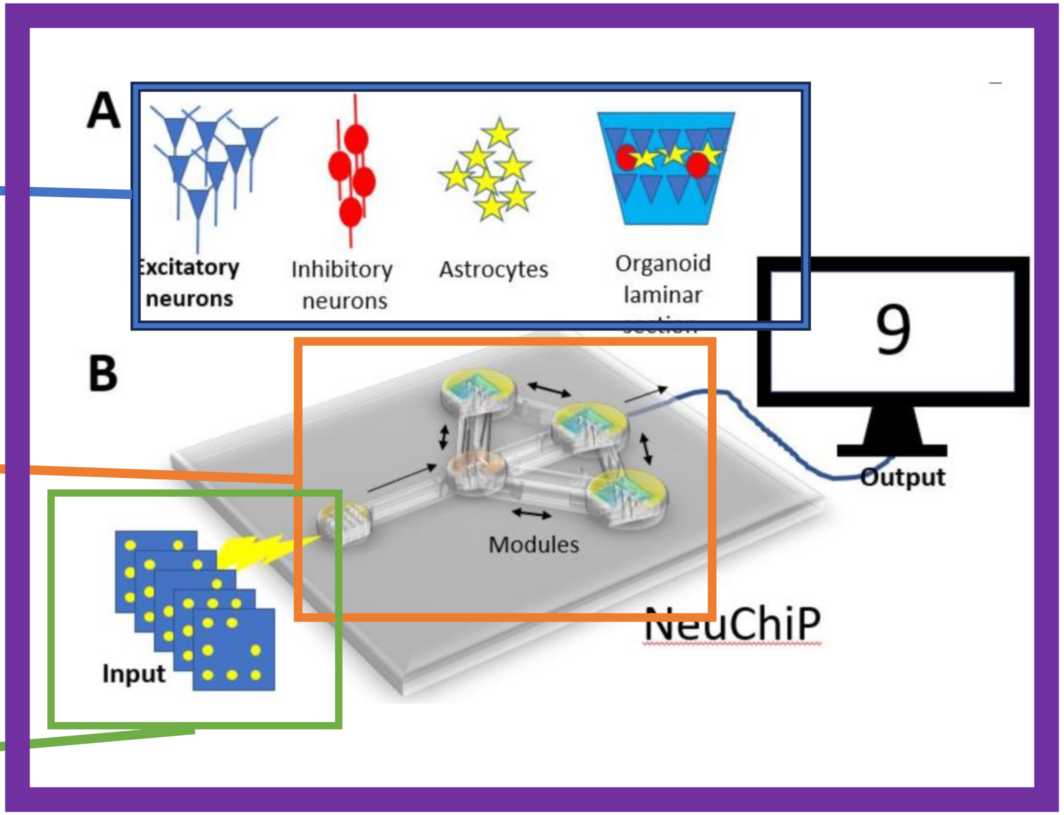
Grow cells



Fabricate Structure



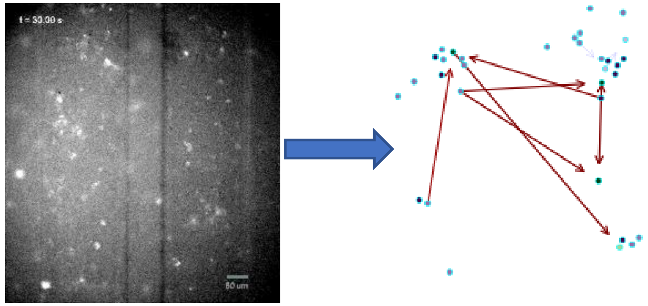
Develop stimulation protocol



Develop models and understanding of emerging structure, learning and plasticity

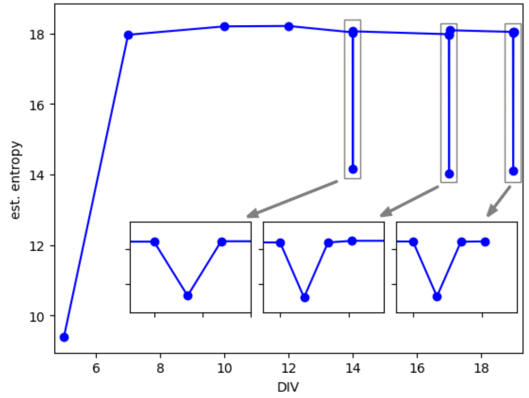
Challenges and tasks

Network functionality



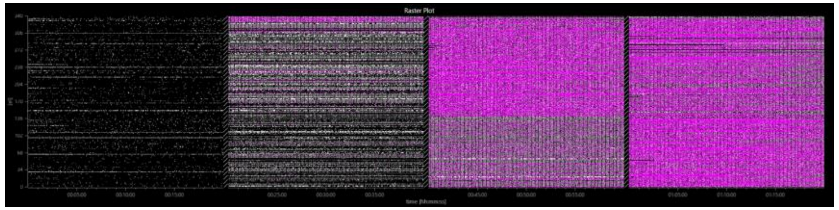
Effective structure inference

Emergence of content

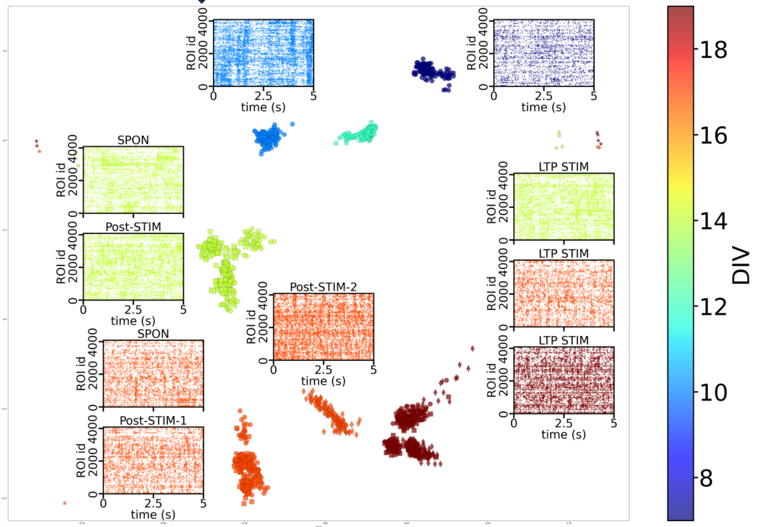


State entropy

Culture Development

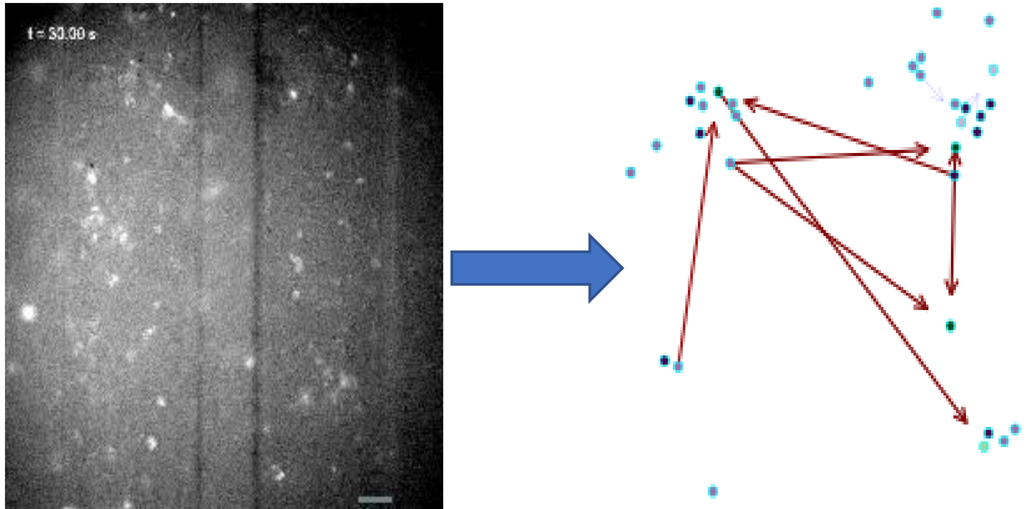


Visual informatics approach



Neuronal network inference

- Inferring effective structure from activity – open question in neuroscience
- Key to understand plasticity and learning dynamics
- Extract current network structure to apply appropriate stimulation strategy
- Gain insight into
  - How neurons interact
  - Functionality of cortical domains
  - Neuronal diseases



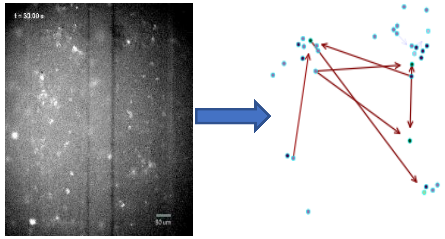
Effective structure

Objectives

e.g. Transfer entropy, correlations

- Existing methods for network inference focus on pairwise causality

- Our method allows for:
  - ✓ inferring excitatory and inhibitory *nature of neurons* and signals
  - ✓ identify *link existence*
  - ✓ consider *interactions between multiple neurons*
  - ✓ network activity *prediction*



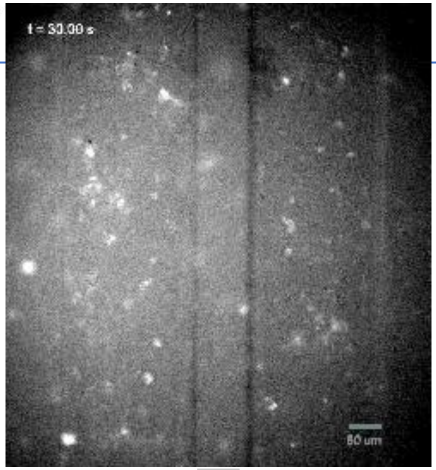
Excitatory neurons stimulate neighbors to spike

Spike! higher spiking probability

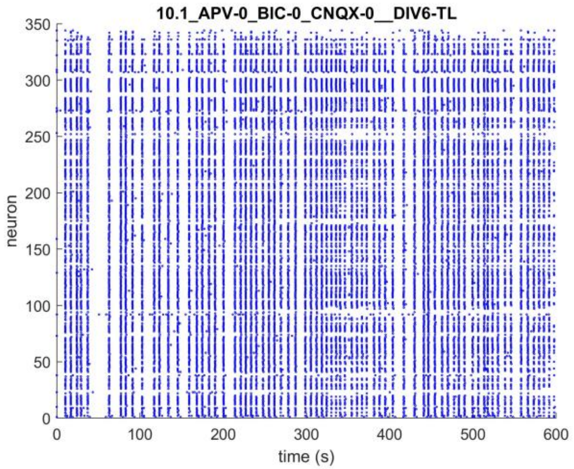
Inhibitory neurons prevent neighbors from spiking

Spike! lower spiking probability

Model – inverse Ising



Neural activities (Raster plot)



Data: which neuron is firing at time t

<u>Model:</u>

- Mapping onto kinetic Ising model:

  $P(s_i^t|\boldsymbol{s}^{t-1}) \propto \exp[(H_i + \sum_j J_{ij} s_j^{t-1}) s_i^t]$

  - $s_i^t = \pm 1$: activity of i at time t
  - J_{ij}: effective <u>synaptic strength</u> from j to i
  - H_i : <u>background activity</u> of i

- Introducing latent variables describe:
  - z_j: <u>neuronal nature</u> of neuron j
  - ϕ_{ij}: <u>existence of link</u> from j to i

- Prior distributions and information:
  - Information we guess/know (structure)
  - Hyperparameters: ρ

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Inference algorithm

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- Employ generalized maximum likelihood (GML) estimation with two-layered expectation maximization (EM):

Macro E-Step (Effective Structure):

Evaluate:

$$\mathbf{J}^*,\, \mathbf{H}^* = \underset{\boldsymbol{J},\, \boldsymbol{H}}{\operatorname{argmax}} \ \ln P\left(\boldsymbol{s}, \boldsymbol{J}, \boldsymbol{H} \,|\, \boldsymbol{\rho}^{\Xi}\right)$$

↓ $\mathbf{J}^*, \mathbf{H}^*$ ↑ $\boldsymbol{\rho}^{\Xi}$

Macro M-Step (Hyperparameters):

Micro E-Step (Latent Variables):

Evaluate $P_{old}(\phi_{ij}), P_{old}(z_j), \ \forall i, j$

⇄

Micro M-Step:

1. Find optimal $\boldsymbol{\rho}^{\Xi}$
2. Replace $\boldsymbol{\rho}_{old}$ by $\boldsymbol{\rho}^{\Xi}$

- When converged, we get:
  1. Effective coupling strengths (J_{ij})
  2. Neuronal nature
  3. Effective connectivity

GML:

Optimize the evidence function

$$\ln P(\boldsymbol{s}|\boldsymbol{\rho})$$

Model:

- Mapping onto kinetic Ising model:

$$P\left(s_i^t \middle| \boldsymbol{s}^{t-1}\right) \propto \exp\left[\left(H_i + \sum_j J_{ij} s_j^{t-1}\right) s_i^t\right]$$

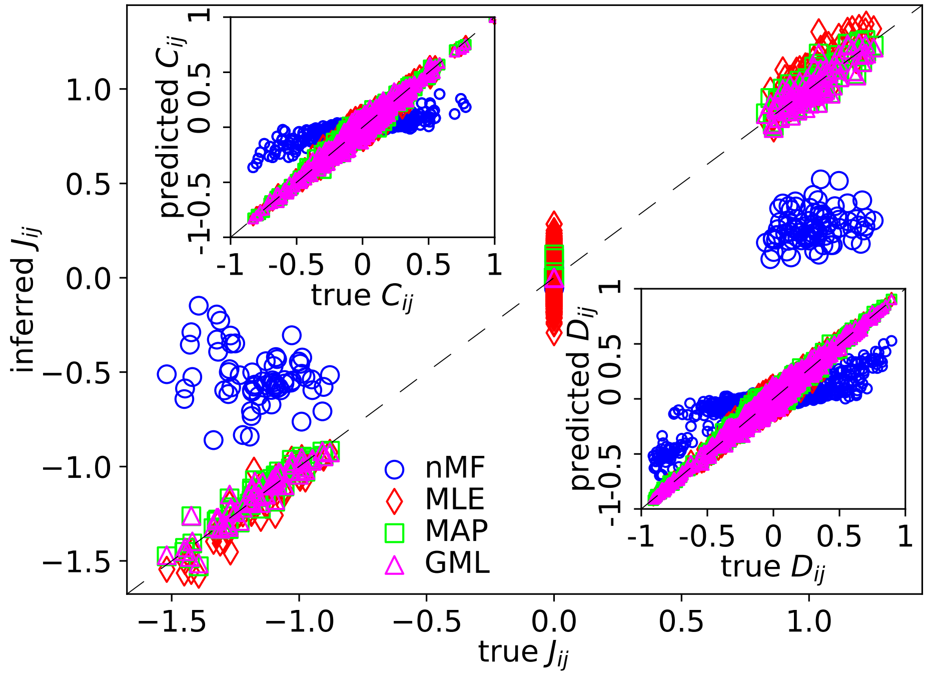
- latent variables: z_j, ϕ_{ij}
- Priors (hyperparameters ρ)

Synthetic data - inference

- Synthetic data are generated to validate our method
- J_{ij} follows mixture of three distributions: (large positive/zero/large negative)
- Compare results using:
  1. Naïve mean field (nMF)
  2. Maximum Likelihood Estimation (MLE)
  3. Maximum a posteriori (MAP, one macro iteration of GML)
  4. Generalized maximum likelihood (GML)

<u>For inferred J_{ij}:</u>

- nMF perform badly
  - as J_{ij} are <u>not Gaussian with zero mean and small variance</u>
- MLE is good in general, yet unable to identify zeros
- MAP identifies almost all zero J_{ij}
- GML identifies all J_{ij} types correctly



Main figure: inferred J_{ij} vs true J_{ij}

Synthetic data - prediction

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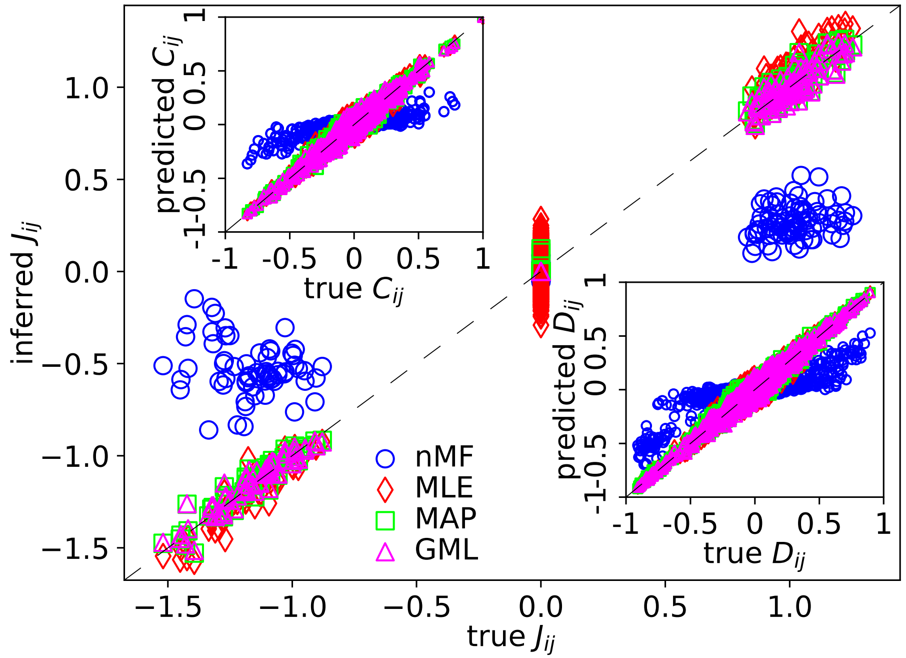
Predicting activities:

- Predicting activity data using Monte-Carlo simulations
- Evaluate equal + delayed time covariance for comparison
- nMF perform poorly
- MAP and GML perform as good as MLE



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Top inset: equal time covariance:

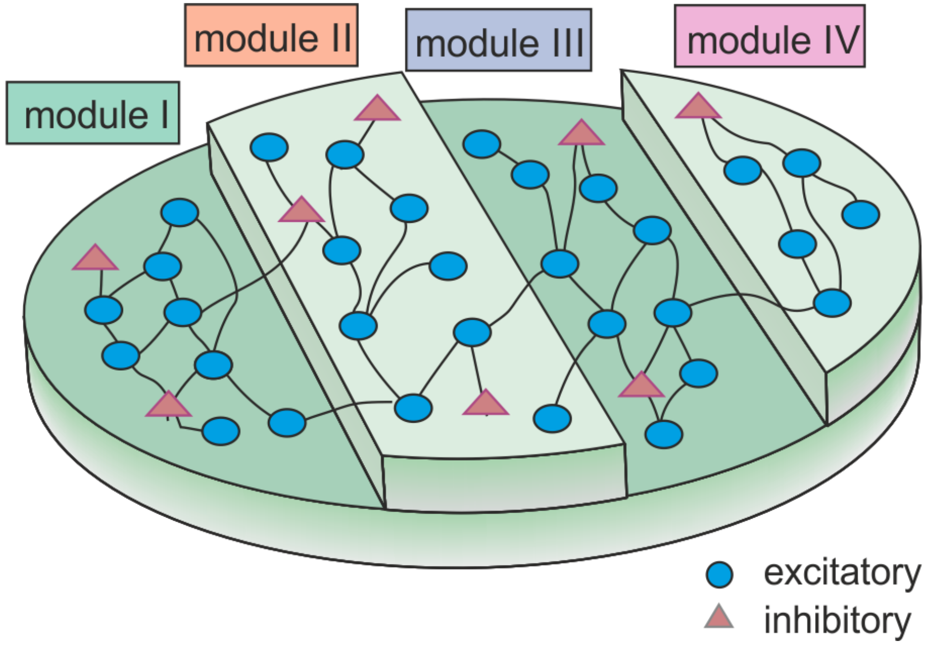
$$C_{ij} = \langle (s_i(t) - m_i)(s_j(t) - m_j) \rangle_t$$

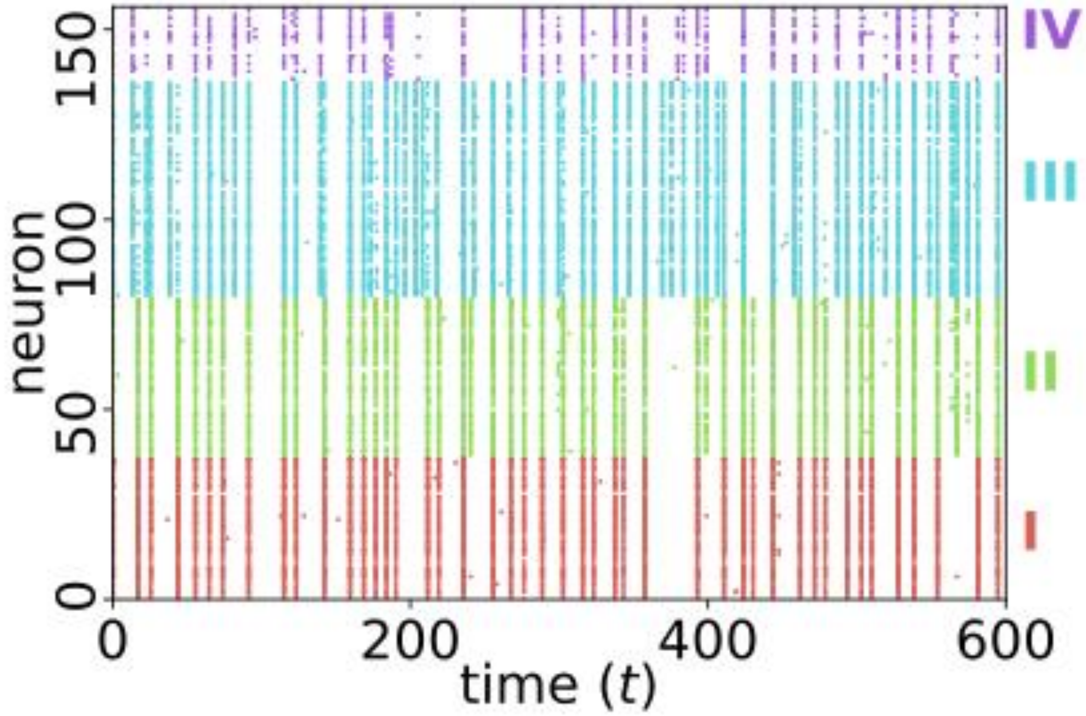
Bottom inset: delayed time covariance:

$$D_{ij} = \langle (s_i(t) - m_i)(s_j(t-1) - m_j) \rangle_t$$

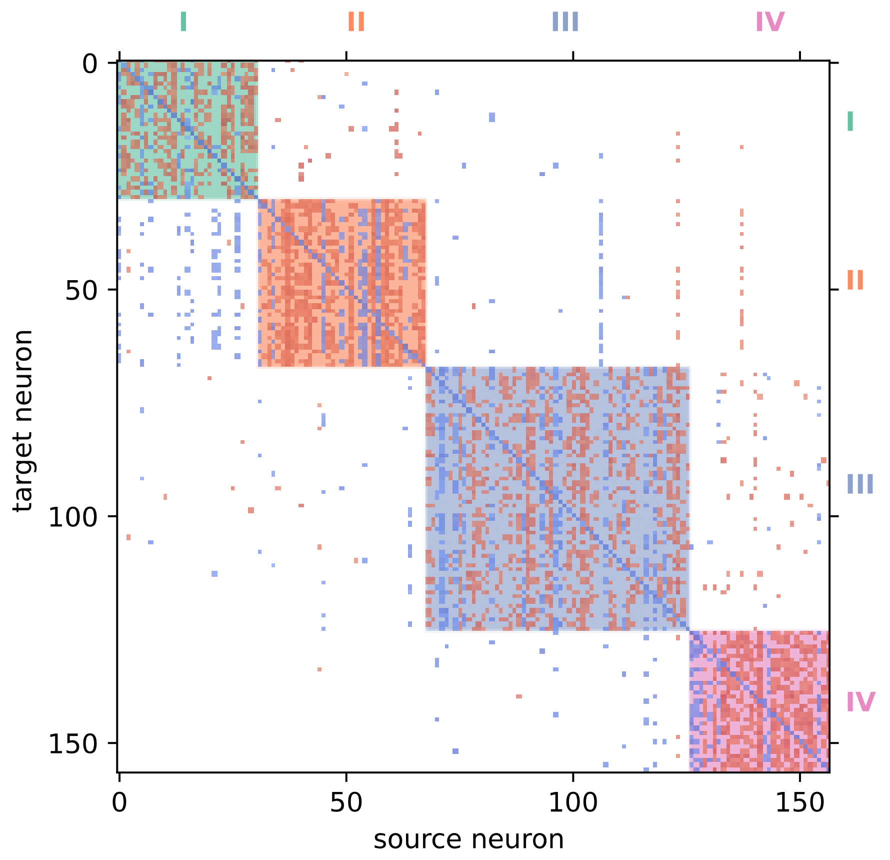
In-silico (neuronal emulator) data

- In-silico neuronal activities (157 neurons)
- Excitatory : Inhibitory = 8:2 (similar to brain cortex)
- Stripes pattern substrates
- Activities generated by neuronal emulator (University of Barcelona)

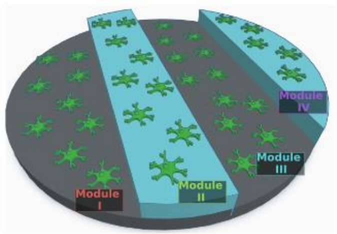




Inferred structure -emulator data



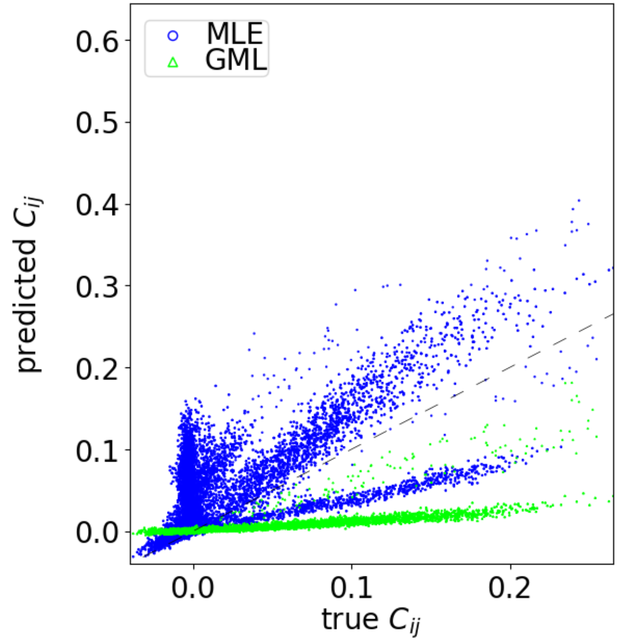
weighted adjacency matrix of J_{ij}



- Inferred network shows strong clustering effect:
  ⇒agrees with true model
- Positive predictability of identifying *neuronal types*:
  ⭐ Excitatory: 96% (80% for biased random guess)
  ⭐ Inhibitory: 64% (20% for biased random guess)
  ⇒ Overall: 87% (68% for random guess)
- Identifying *effective links*:
  ⭐ True positive rate (TPR) = 81.2%
  ⭐ False positive rate (FPR) = 9.2%
  (For GTE, TPR = 50.8% when FPR = 9.2%)

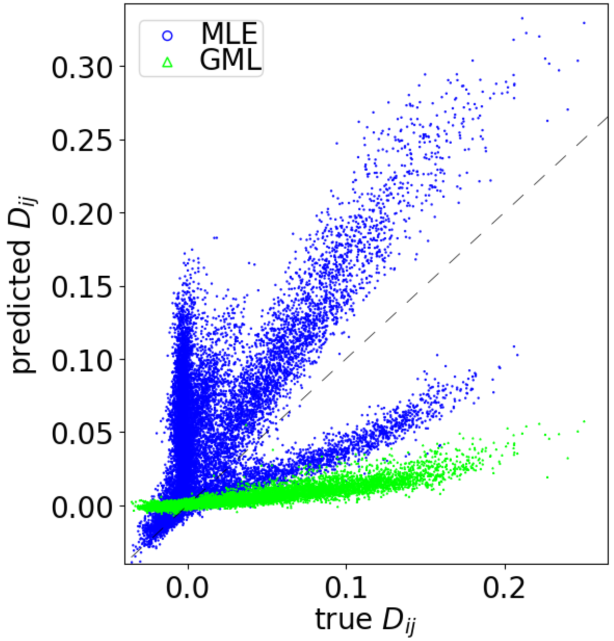
prior information

In-silico activities prediction



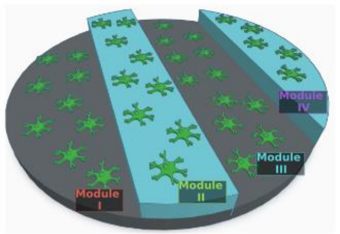
equal time covariance

$$C_{ij} = \langle (s_i(t) - m_i)(s_j(t) - m_j) \rangle_t$$



delayed time covariance

$$D_{ij} = \langle (s_i(t) - m_i)(s_j(t-1) - m_j) \rangle_t$$



Compare results of:
- MLE
- GML

- ➢ Data prediction is produced using Monte-Carlo simulations
- ➢ Same trend as MLE
- ➢ Small values may result of the restrictions from priors

In-vitro primary culture results

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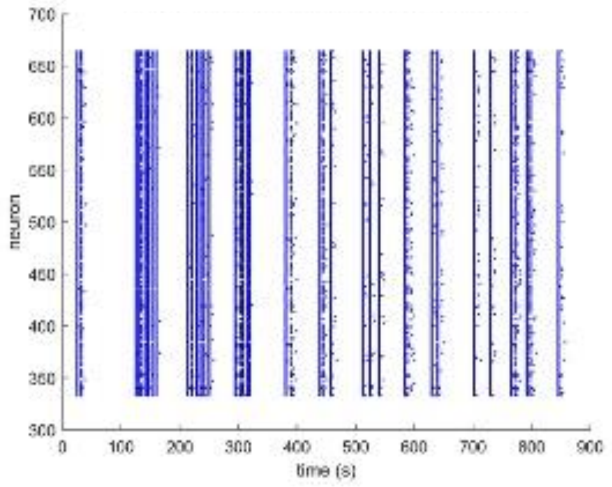
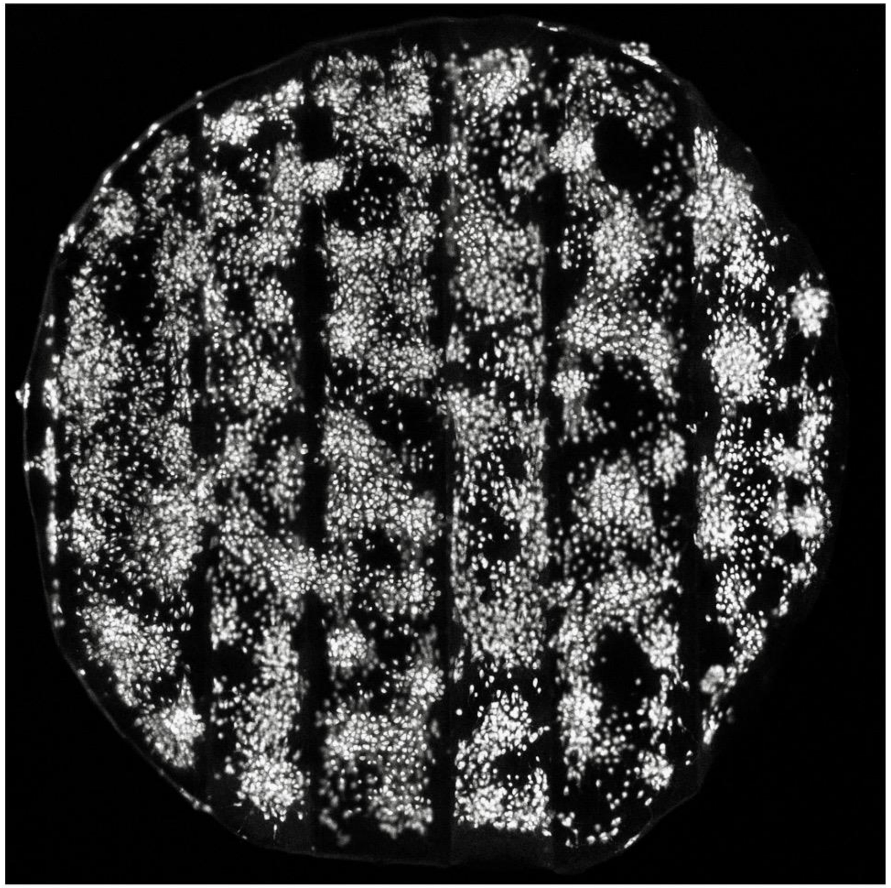
Experimental setup

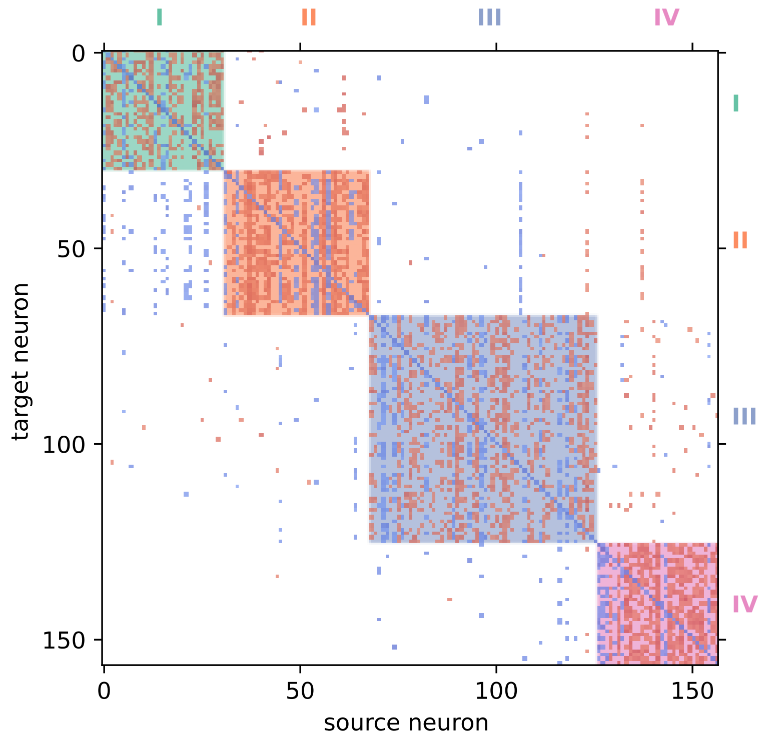
- Rat cortical neuronal network
- Pattern substrates same as last experiment
- Supress connectivity across stripes



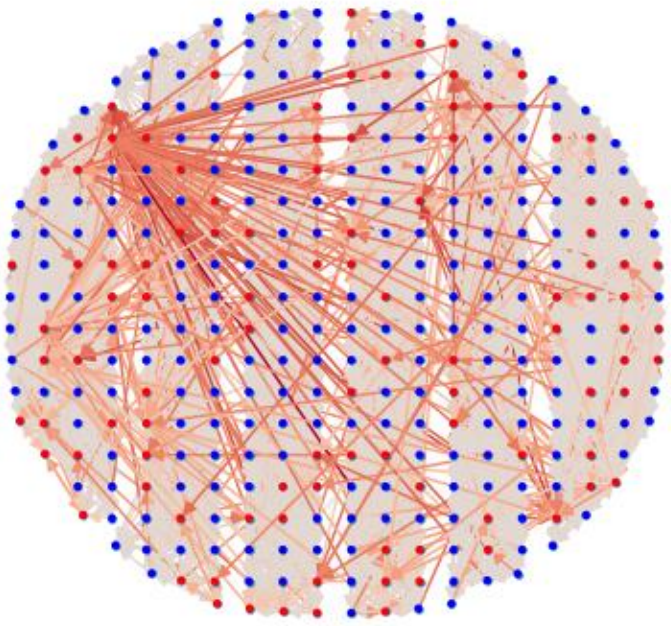
Spontaneous activities recording on days in-vitro (DIV) 17



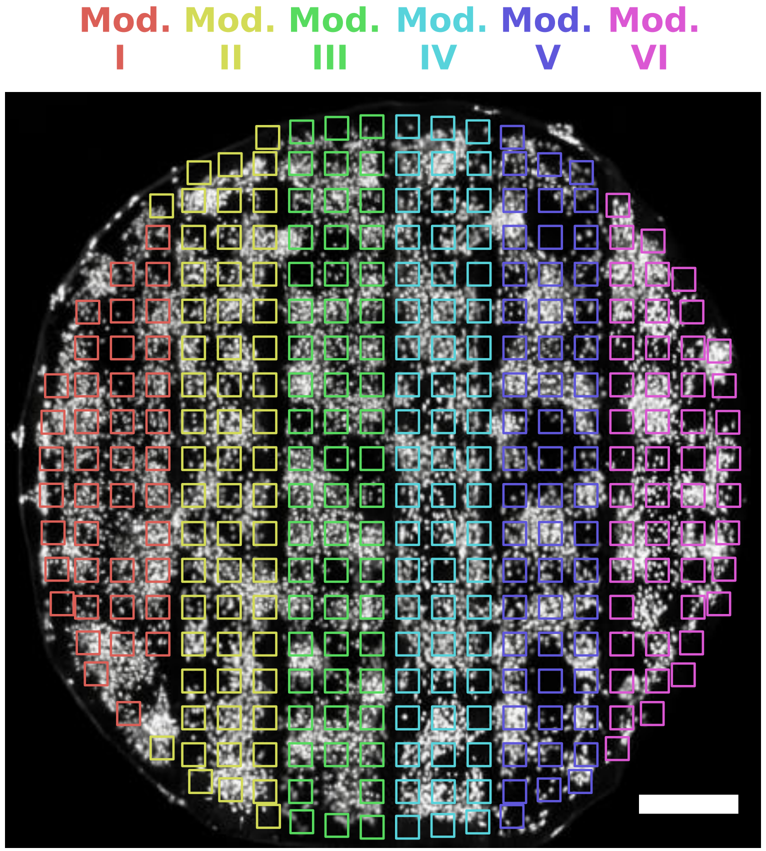
Inferred structure - real data



weighted adjacency matrix of J_{ij}

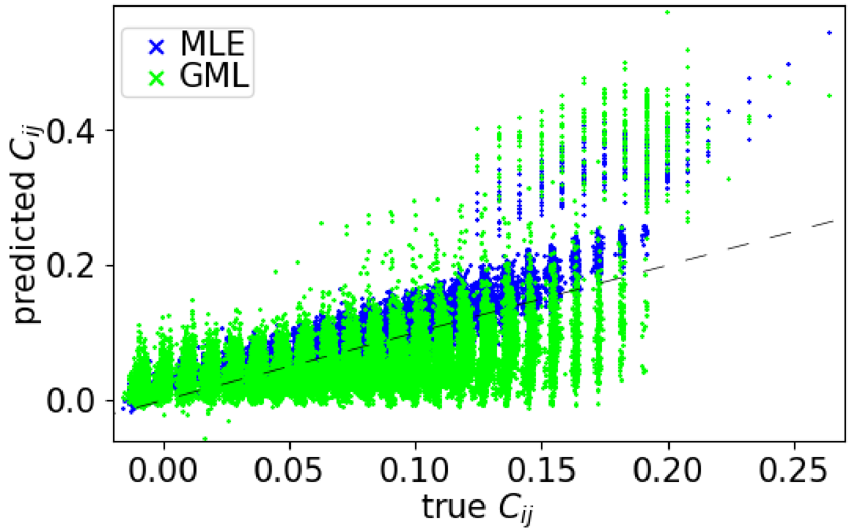


Effective network
Edges color: J_{ij}
Node color: Neuron type



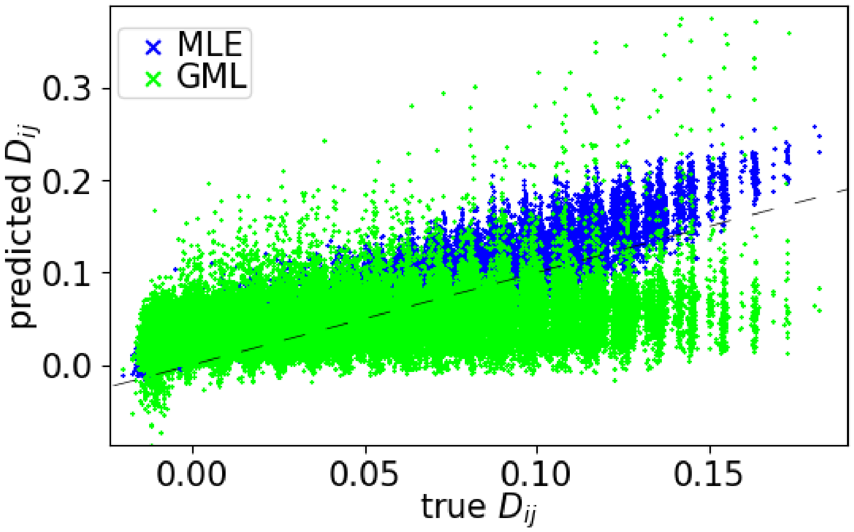
- Infer J_{ij} using GML
- Strong clustering effect
- Neuronal nature

Predicting in-vitro activities



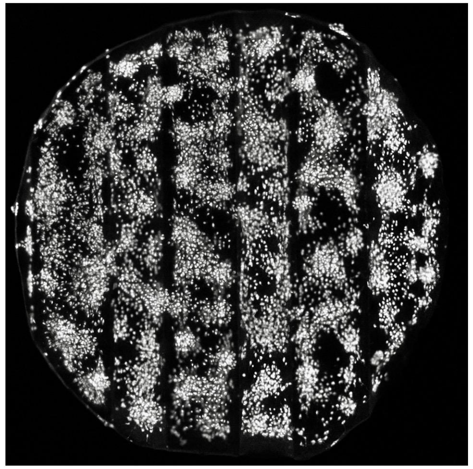
equal time covariance

$$C_{ij} = \langle (s_i(t) - m_i)(s_j(t) - m_j) \rangle_t$$



delayed time covariance

$$D_{ij} = \langle (s_i(t) - m_i)(s_j(t-1) - m_j) \rangle_t$$



- Similar results to in-silico test
- Method works well on real data

Visual Informatics

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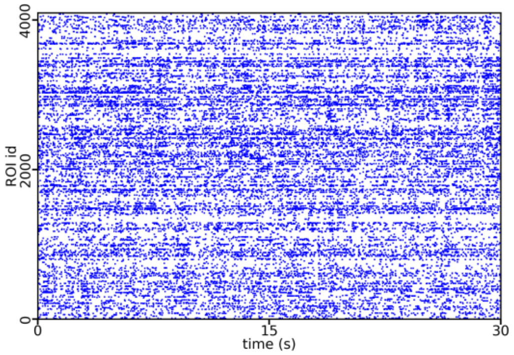
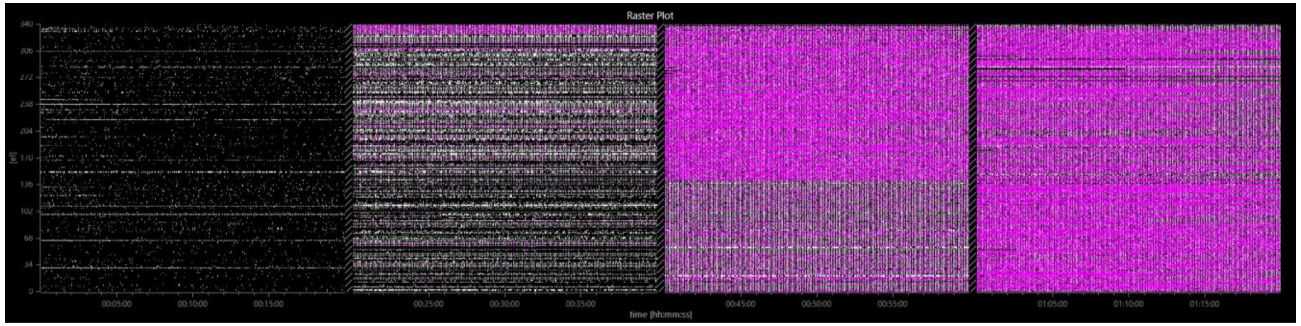
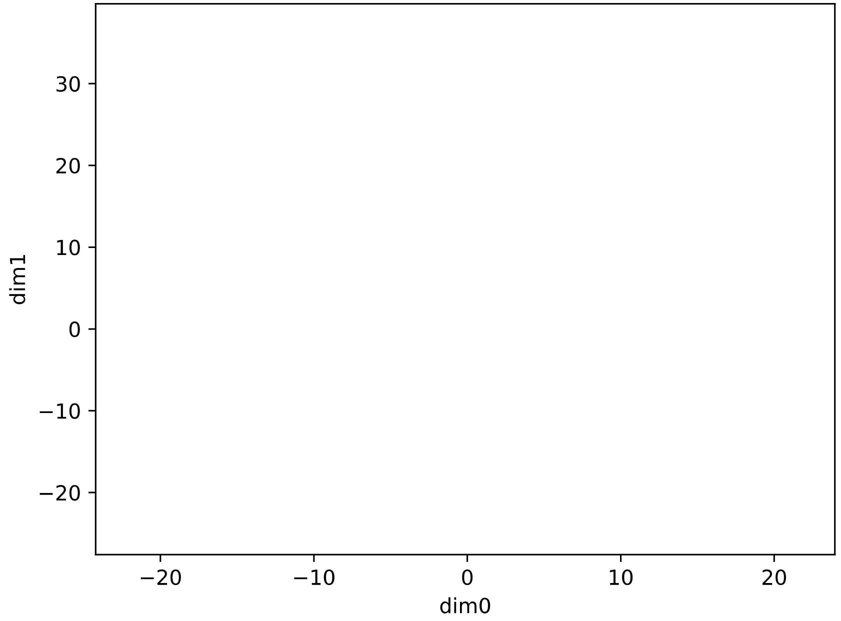
- Neuronal systems are in extreme high dimensions:
  - Culture of N neurons, there are 2^N possible firing patterns
  - Hard to gain insights from raster plots



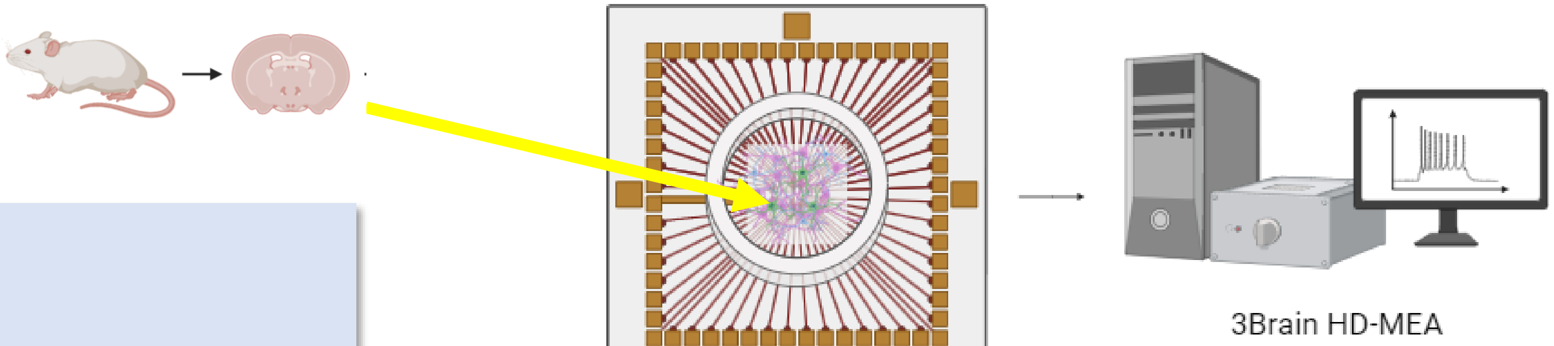
- Visual informatics approach:
  - Create intuitive visual 2D representation of high dimensional data
  - Facilitate understanding and analysis of complex data
    e.g. culture development, response to stimulation



DIV 5 DIV 10 DIV 14 DIV 19

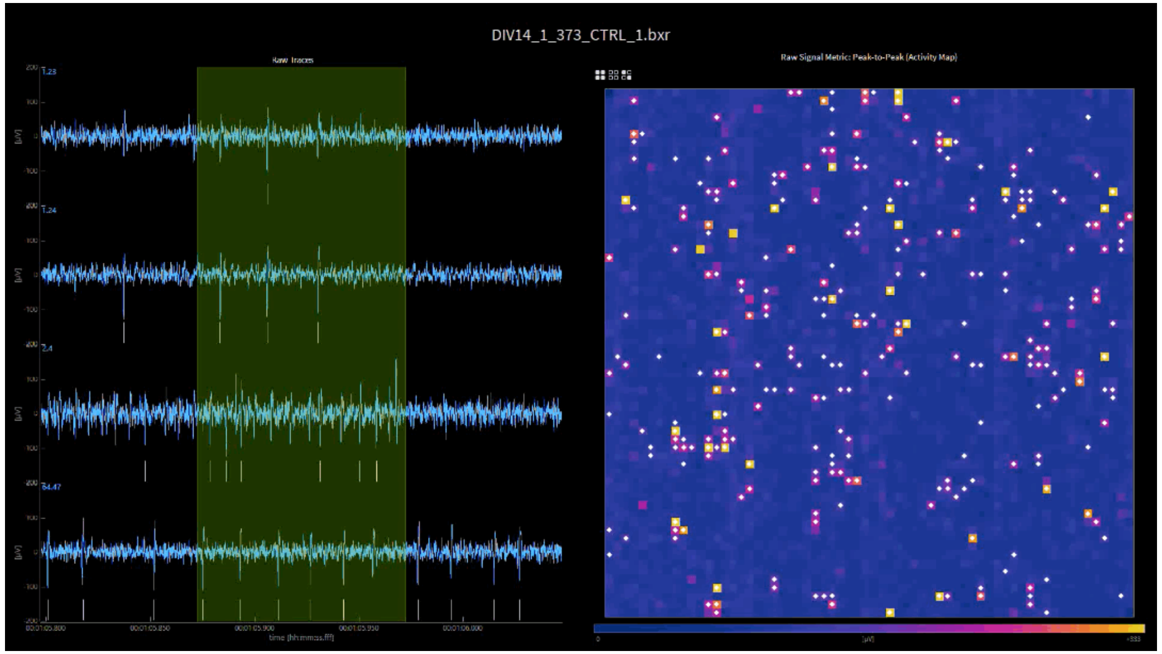


Visual Informatics - results



The Data

- Primary mouse cortical culture
- put on multi-electrode array (MEA) devices
- Activity data being recorded on different days
- Before day 14:
  - only spontaneous
- After day 14:
  - spontaneous -> stimulation -> post-stimulation



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Dimensionality reduction

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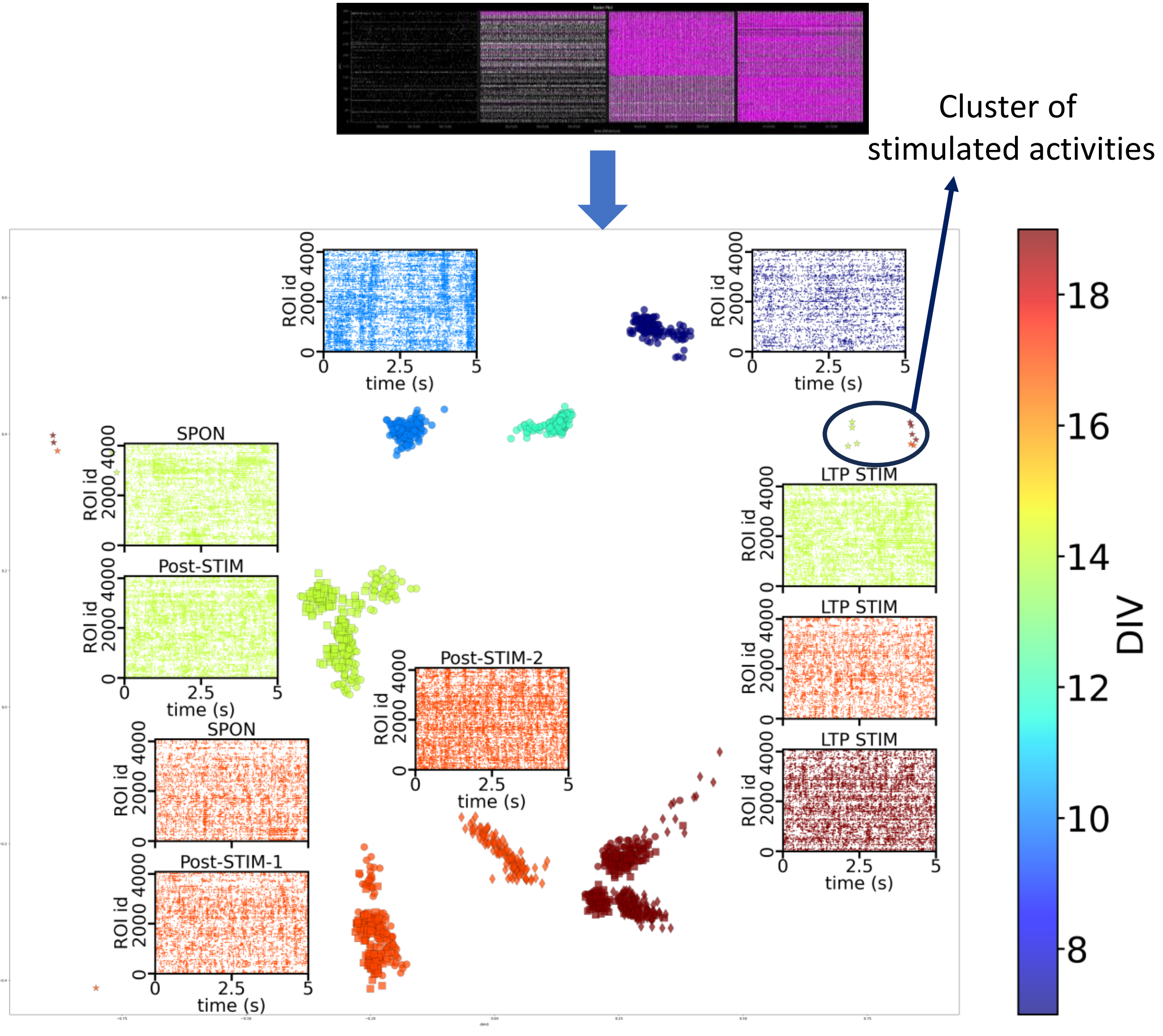
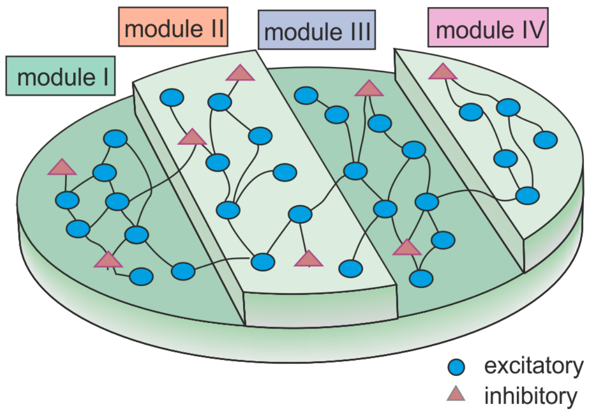
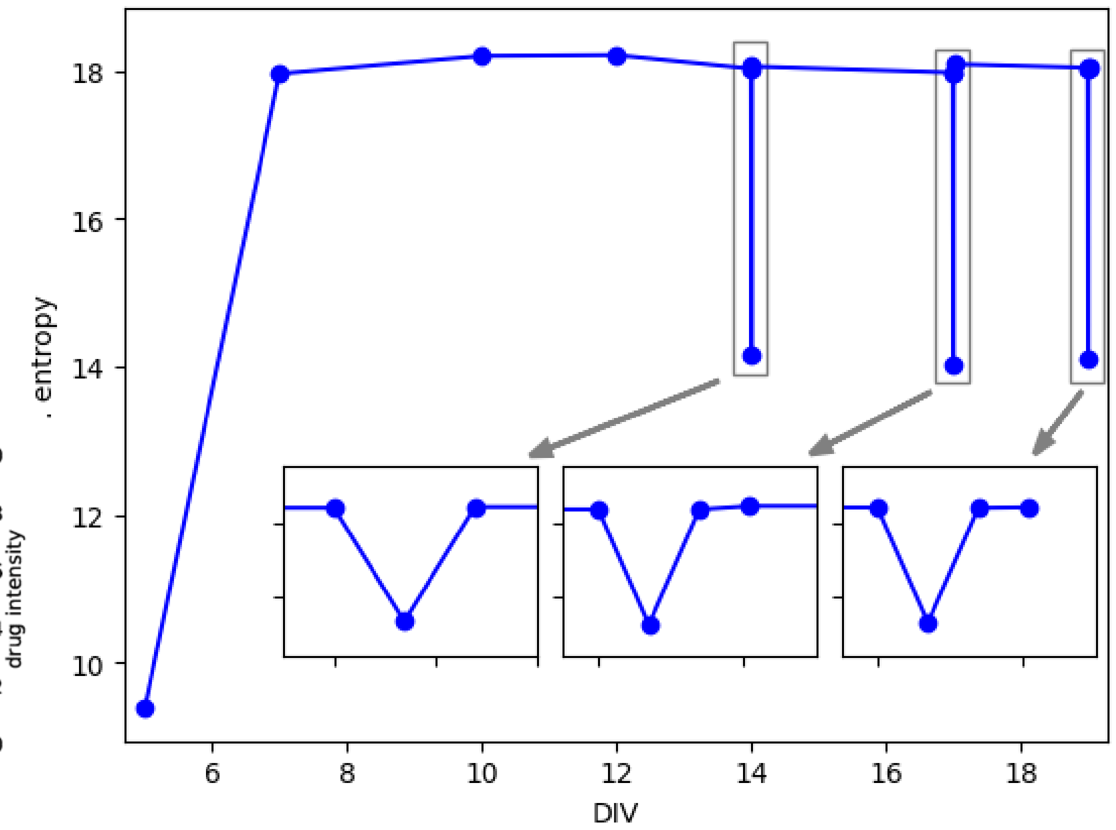
- Apply minimum distortion embedding (MDE):
  - similar to t-SNE
  - retains global structure and relative distances
  - works better on large dataset
- Activities from different recordings form distinct clusters
- Most stimulated activities form a cohesive cluster
  - exhibits similar behavioral responses under stimulation



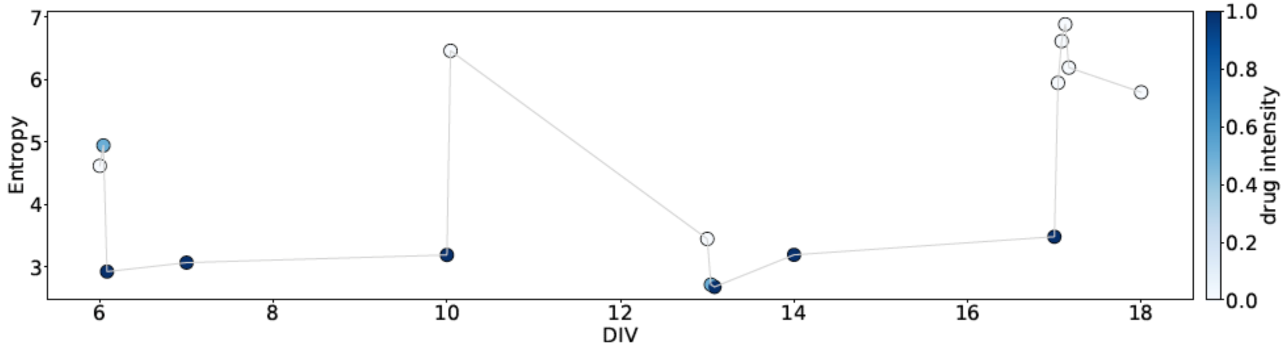
Entropy drop under stimulation



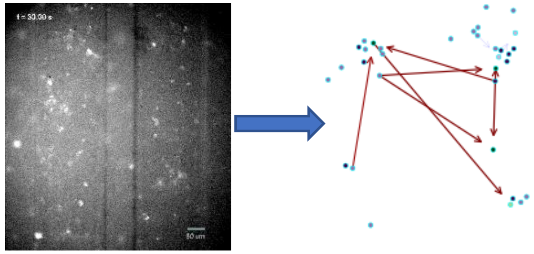
Activity under stimulation



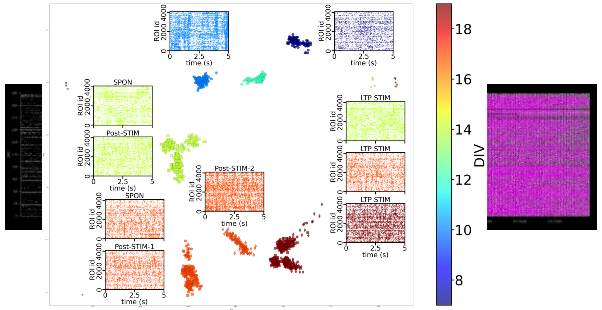
Suppressing activity



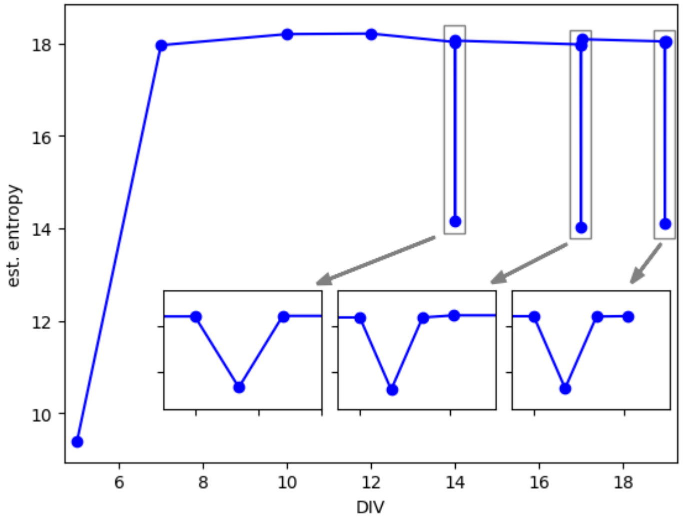
Summary



- ✓ Extended inverse Ising model for inference in neuronal networks
- ✓ Inferring neuronal nature, effective connections, as well as effective synaptic strength
- ✓ Validates on *synthetic, in-silico* and *in-vitro* data



- ✓ MDE for dimensionality reduction
- ✓ *Clear separation of clusters* in reduced dimensional space
- ✓ Shows neuronal activities have similar behavioral responses under stimulation



- ➢ Entropy dropped under stimulation
- ➢ Looking for a strong *plasticity* effect