NIPS 2015 Workshop: Modelling and Inference for Dynamics on Complex Interaction Networks

Inference of Neural Circuit Connectivity from High-dimensional Activity Recording Data: A Survey

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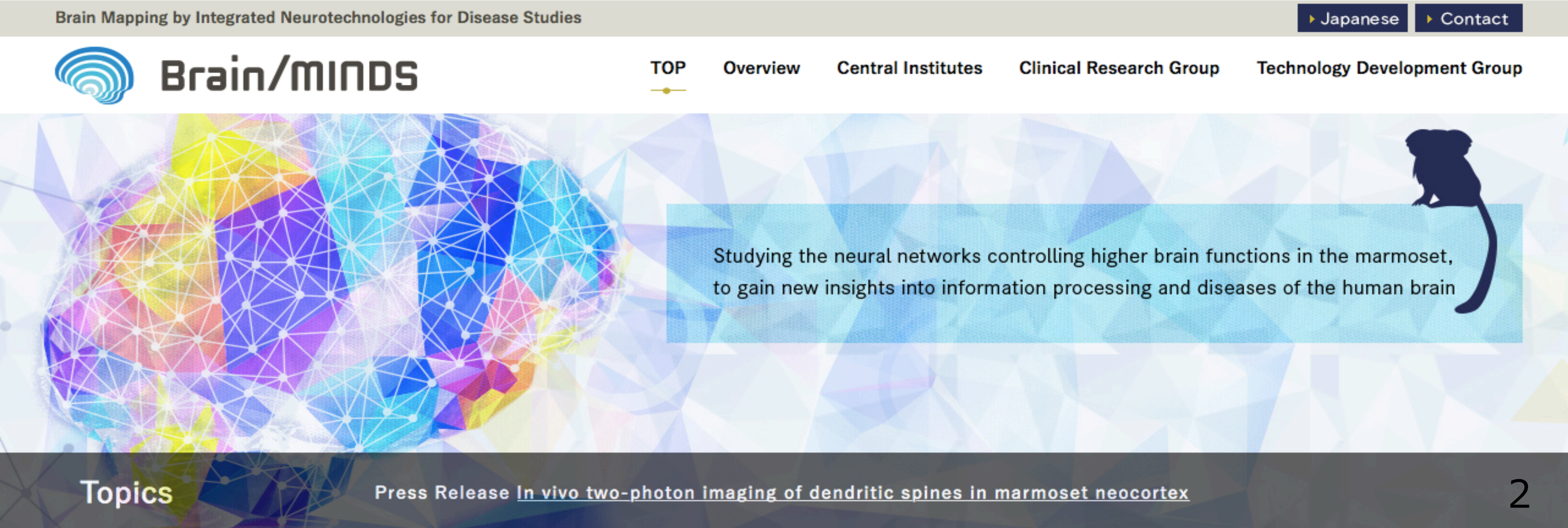
Brain/MINDS Program (2014~2023)

- Structural/Functional maps of marmoset brain
  - RIKEN + 22 labs in Japan
  - 3 billion yen (~$30M)/year
  - OIST: data-driven model building

brainminds.jp

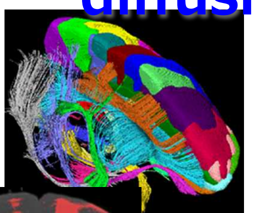


Multi-scale Neural Modeling

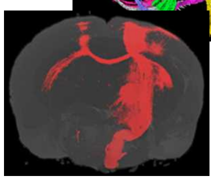
Structural Map

structural MRI

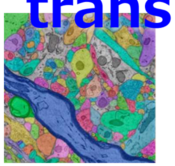
diffusion MRI



tracers



transparent brain



serial section EM

Neural Models

Macroscopic

whole brain connectome

population rate models

<u>behaviors and cognition</u>

Mesoscopic

cell types, synaptic dynamics

spiking neuron models

<u>computation in each area</u>

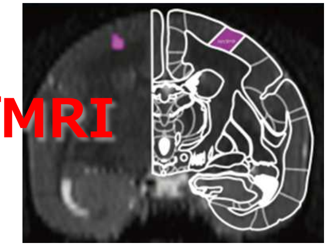
Microscopic

dendrites, ion channels

conductance/pathway models

<u>cellular/molecular mechanisms</u>

Functional Map

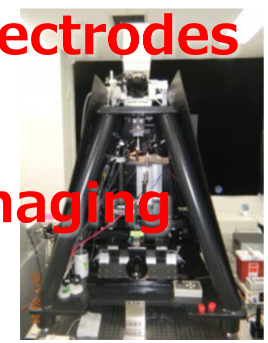


task fMRI

resting fMRI

ECoG

multi-electrodes



Ca2+ imaging

molecular imaging

Introduction

Why Neural Circuit Inference?

- To uncover dynamics/algorithms behind neural representation
  - whole brain: functional MRI, MEG, EEG,...
  - local circuit: multi-electrode, optical recording
- Anatomical identification of all connections is costly/impractical/imprecise

This Survey: Local Circuit Inference

- Data processing pipeline
- Biophysical and technical challenges

Data Processing Pipeline

Data acquisition → Pre-processing → **Network inference** → Post-inference → Validation

Data acquisition

Calcium imaging
- 1000s of neurons
- Good time resolution
- Complex pre-processing

Multiple electrodes
- Very good time resolution
- Few 100s
- Mixed signals
- Highly invasive

Pre-processing

Calcium imaging
- Neuron image segmentation
- Fluorescence trace extraction
- Spike train inference

Multiple electrodes
- Sorting required

Network inference

Model-free:
- Correlation
- Transfer entropy
- Deep learning
- …

Model-based:
- Generalized linear models
- Max. entropy
- Hawkes processes
- …

Post-inference
- Confounded effects
- Matrixes combination
- Edge orientation

Validation

Simulated vs real data

Model-free Approaches

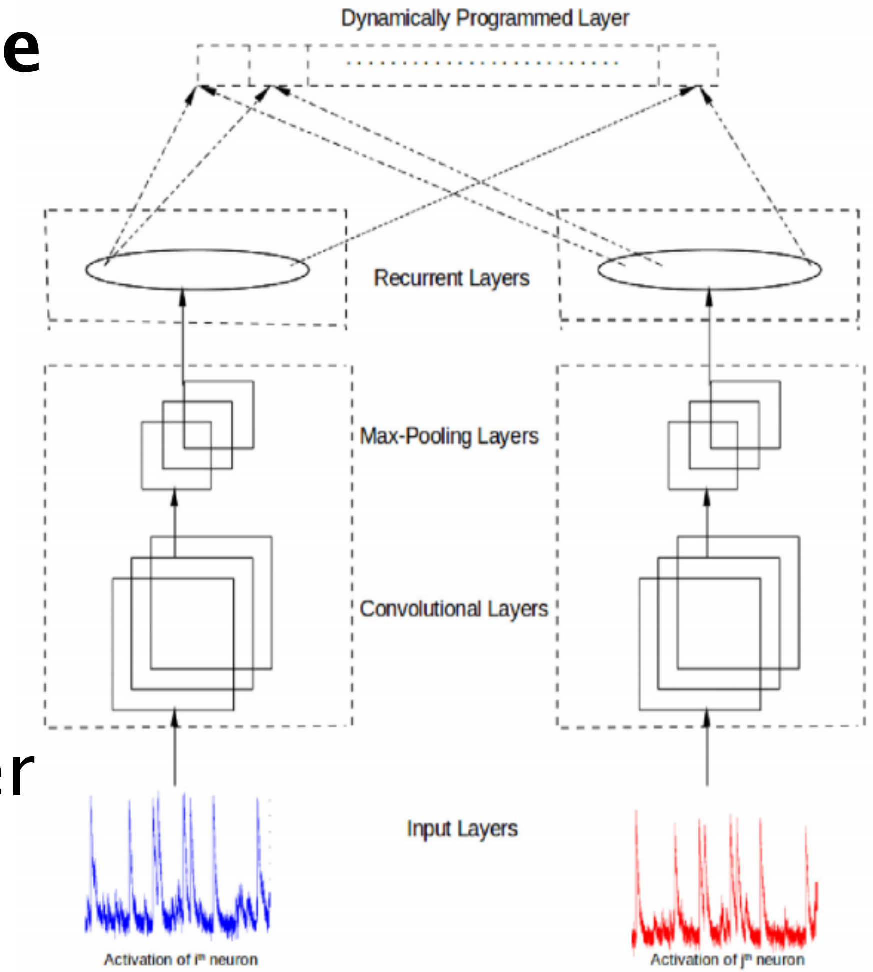
- Descriptive statistics
  - correlation $$\rho_{X,Y} = \mathrm{corr}(X,Y) = \frac{\mathrm{cov}(X,Y)}{\sigma_x \sigma_y} = \frac{E[(X-\mu_x)(Y-\mu_y)]}{\sigma_x \sigma_y}$$
  - cross correlation $$\rho_{Y \to X}(\tau) = \frac{E[(Y_t - \mu_y)(X_{t+\tau} - \mu_x)]}{\sigma_x \sigma_y}$$
  - coincidence index $$CI = \frac{\sum_{d=0}^{r} \rho_{X,Y}(d)}{\sum_{d=0}^{T} \rho_{X,Y}(d)}$$
  - partial correlation $$PC_{i,j} = \frac{\sum_{ij}^{-1}}{\sqrt{\sum_{ii}^{-1} \sum_{jj}^{-1}}}$$
- Information theoretic methods
  - transfer entropy $$TE_{Y \to X} = \sum_{x_{t+1}, x_t^k, y_t^l} P(x_{t+1}, x_t^k, y_t^l) \log_2 \frac{P(x_{t+1} | x_t^k, y_t^l)}{P(x_{t+1} | x_t^k)}$$
  - information gain $$IG_{Y \to X} = G(x_{t+1}) - G(x_{t+1} | y_t)$$

Deep Learning Approach

(Veeriah et al. 2015)

Integrated architecture for spike and connection inference

- Convolutional neural network
  - identify relevant events in fluorescence time series
  - with temporal tolerance
- Recurrent Neural Network
  - model temporal sequences of relevant events
- Dynamically programmed layer
  - compute connection probability



Model-based Approaches

- Generative models
  - auto-regressive (AR) $$x_i(t) \quad = \quad A_{i0} + \sum_{j=1}^{P} \sum_{k=1}^{K} A_{ij}(k) x_j(t-k) + \epsilon_i(t),$$
  - generalized linear (GLM) $$x_i(t) \sim \mathrm{Ber}(\cdot|\rho_i(t))$$ $$\rho_i(t) \equiv \phi\left(A_{i0} + \sum_{j=1}^{P} \sum_{k=1}^{K} A_{ij}(k) x_j(t-k) \right)$$

    e.g. stochastic integrate & fire
- Inference
  - maximum likelihood $$\theta^* = \underset{\theta}{\operatorname{argmin}}\, J(\theta|D)$$
  - Bayesian $$\theta^* = \underset{\theta}{\operatorname{argmin}} \{J(\theta|D) + \lambda \mathcal{R}(\theta)\}$$

    regularizers $$\mathcal{R}(\theta) = \sum_r \theta_r^2 \qquad \mathcal{R}(\theta) = \sum_r |\theta_r|$$

Neural and Ca^{2+} Dynamics Model

(Mishchenko et al. 2011; Fletcher et al 2014)

- Generative model $\tilde{v}_i^{k+1} = (1-\alpha_{IF})v_i^k + \sum^N W_{ij} s_j^{k-\delta} + d_{v_i}^k$
  - stochastic IF $(v_i^{k+1}, s_i^{k+1}) = \begin{cases} (\tilde{v}_i^k, 0) & \text{if } v_i^k < \mu \\ (0, 1) & \text{if } \tilde{v}_i^k \geq \mu \end{cases}$
  - calcium dynamics $z_i^{k+1} = (1-\alpha_{CA,i})z_i^k + s_i^k$
  - fluorescence $y_i^k = a_{CA,i} z_i^k + b_{CA,i} + d_{y_i}^k$
- Inference $\widehat{\theta} = \arg\max_\theta L(\mathbf{y}|\theta) + \lambda \|\mathbf{W}\|_1$
  - parameters $\theta = \{\mathbf{W}, \tau_{IF}, \tau_{CA}, \alpha_{IF}, b_{IF,i}, \alpha_{CA}, a_{CA,i}, b_{CA,i}, i = 1, \ldots, N\}$
  - hidden variables $\mathbf{x} = \{\mathbf{v}, \mathbf{z}, \mathbf{q}, \mathbf{s}\}$
  - E-step: $P(\mathbf{x}|\mathbf{y}, \widehat{\theta}^\ell)$
  - M-step: $\widehat{\theta}^{\ell+1} = \arg\min_\theta \mathbb{E}\left[L(\mathbf{x}, \mathbf{y}|\theta)|\widehat{\theta}^\ell\right] + \phi(\theta)$

Biophysical Challenges

- **Apparent/invisible connection**:
  - common inputs cause apparent connections
  - connection is invisible without neural activity
- **Directionality**: with limited temporal resolution
- **Cellular dynamics**: post-spike adaptation, post-inhibitory rebound, etc.
- **Synaptic dynamics**: short-term adaptation, long-term plasticity, etc.
- **Non-stationarity**: network can shift between multiple states, such as synchronized bursting

Technical Challenges

- **Noise**: electric noise, motion artifacts, etc.
- **Time/space resolution**: calcium image ~100ms
- **Hidden neurons**: e.g., off the focal plane
- **External inputs**: e.g. spontaneous action
- **Prior knowledge**: sparseness, topography, etc.
- **Accuracy**: existence, sign, magnitude, time delay
- **Scalability**: thousands of neurons, millions of potential connections…

Challenges and Solutions

	Data Acquisition	Pre-processing	Connection Inference	Post-inference	Validation
Apparent connection			c1 d12 e12	a3	
Directionality			b123 c1 d12 e12	a2	
Cellular dynamics			c1 d12 e12		
Synaptic dynamics			d12 e12		
Non-stationarity		a123 b2	c1		
Noise		a123 b1 c1	c1 d12 e12		
Time/space resolution			c1 e12		
Hidden neurons					
External inputs					
Prior knowledge			a2 d12 e12		
Accuracy			a23 c1 d12 e12	a3	d1
Scalability			a23		

References

Model-free

- Descriptive statistics
  - a1: Cohen & Kohn, Nat Neurosci, 2011
  - a2: Sutera et al., ECML, 2014
  - a3: Magrans & Nowe, ECML, 2014
- Information theoretic
  - b1: Stetter et al., PLoS Comp Bio, 2012
  - b2: Garofalo et al., PLoS One, 2009
  - b3: Ito et al., PLos One, 2011
- Others
  - c1: Veeriah et al., SIGKDD, 2015

Model-based

- Generalized linear models
  - d1: Pillow et al., Nature, 2008
  - d2: Stevenson et al., IEEE TNSR, 2009
- Spike & calcium dynamics
  - e1: Mishchenko et al., Ann Appl Stat, 2011
  - e2: Fletcher et al., NIPS 2014

Conclusion

- Model-free methods
  - less assumptions, less parameters
  - cannot reproduce dynamics
- Model-based methods
  - needs hyper parameter tuning
  - reproduce dynamics for validation/analysis
- Limitations and opportunities
  - external inputs and hidden neurons
  - non-stationarity
  - cellular/synaptic diversity and scalability