Uncovering representations of sleep-associated hippocampal ensemble spike activity

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Sleep

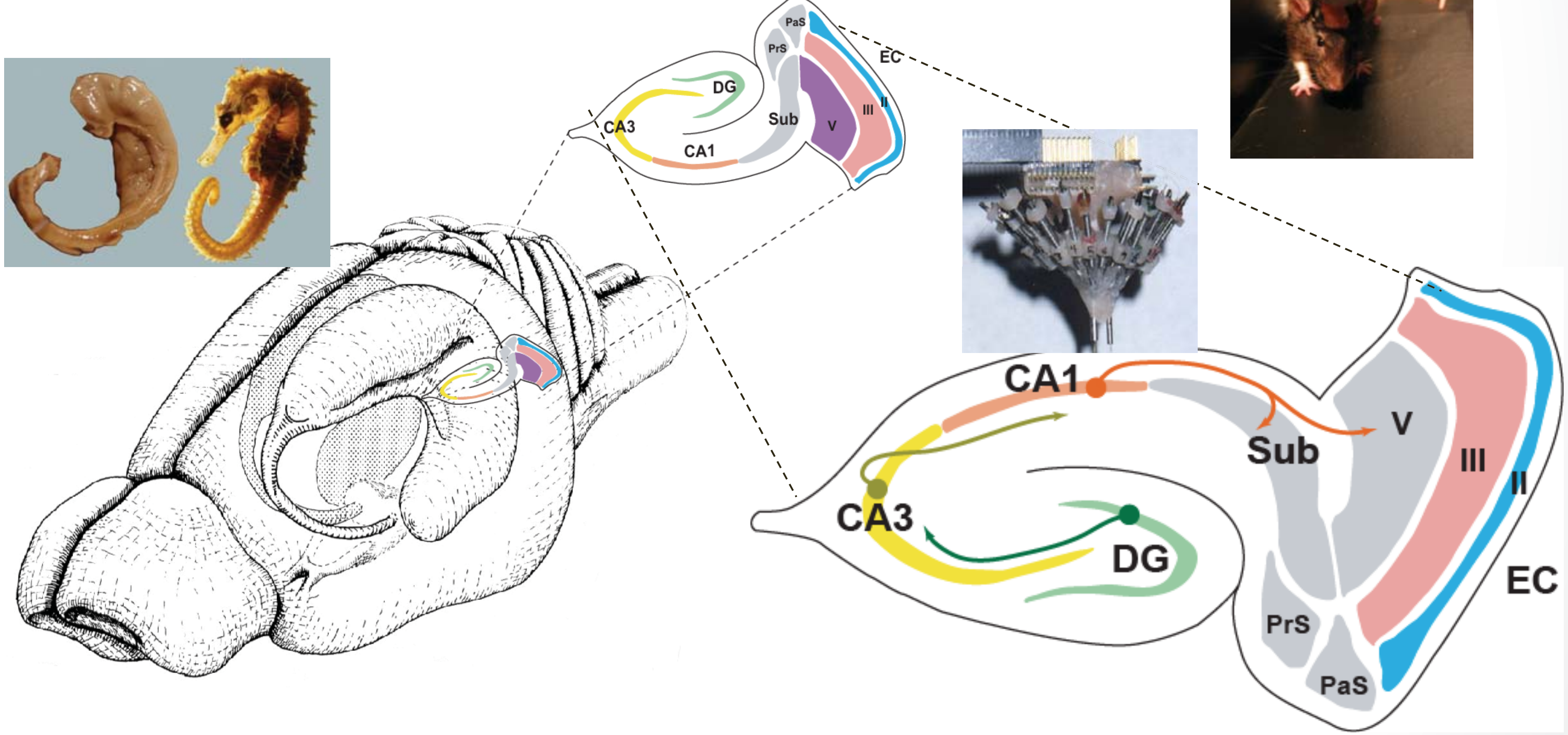
- Promotes memory consolidation (hippocampal memory of wake experiences →neocortex)

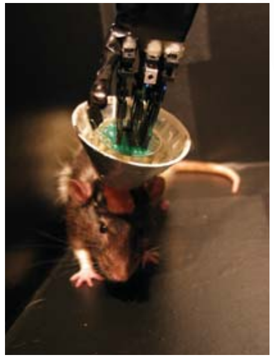
- Sleep deprivation deteriorates attention, learning & memory

- How to decipher the ***content*** of sleep-associated memory ?

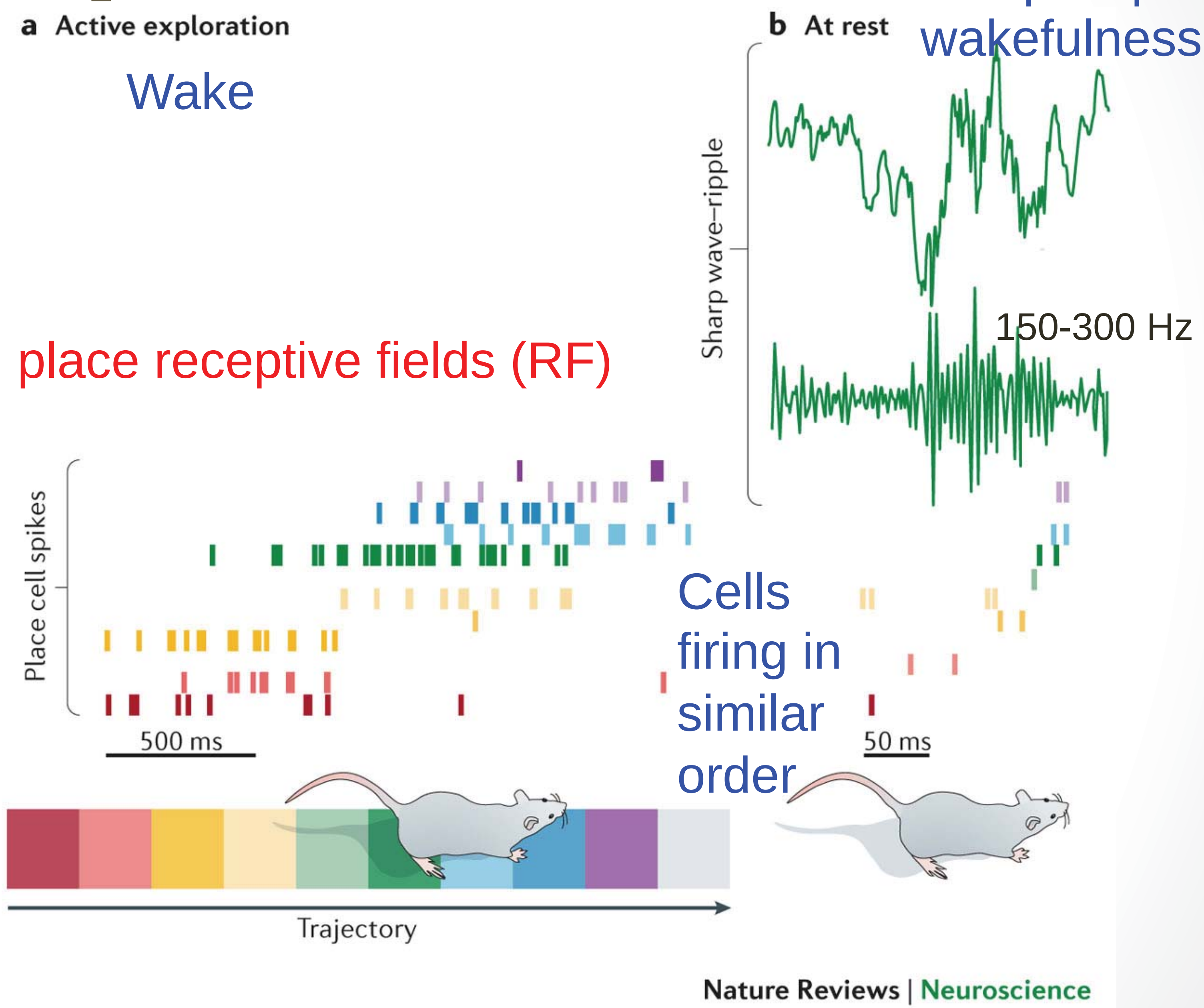
Hippocampus (HPC)

- A model system for studying brain functions of
  spatial & episodic memory
- Large-scale recording of rat dorsal HPC CA1 area





HPC place cells



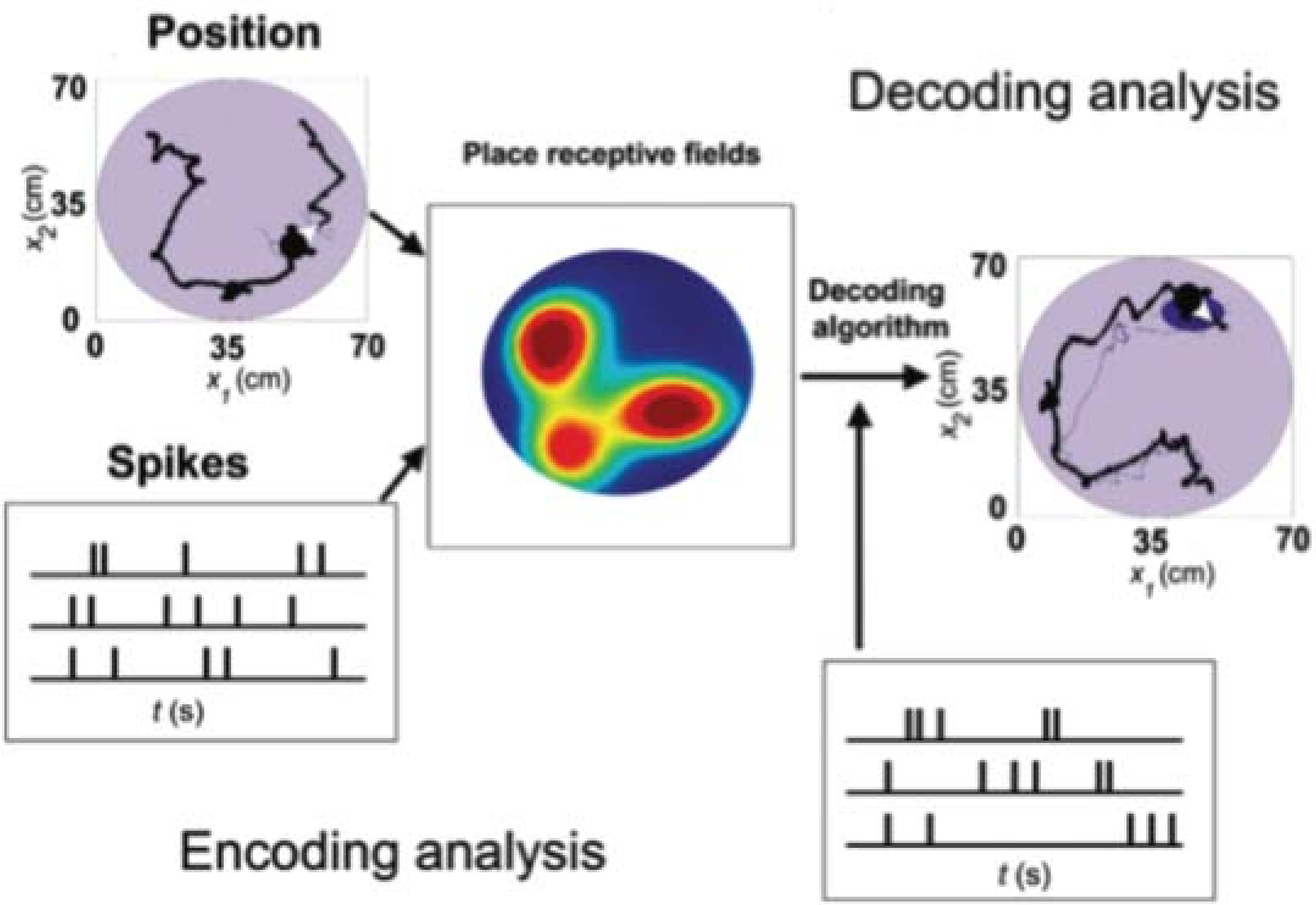
Analysis of population codes in sleep

Non-Content-based	Content-based
Correlation analysis (Wilson & McNaughton, 1994)	Correlation-Principal Component Analysis (Peyrache et al., 2007)
Template Matching (Louise & Wilson, 2001; Euston et al., 2007)	RF-based population decoding (Grosmark & Buzsaki, 2016)
Sequence Matching (Lee & Wilson, 2002, 2004)	RF-free population decoding (Chen, Wilson, et al., 2014, 2016)

Spatial representation

1) **metric & topographic** (location-based)

Decode$_{wRF}$: based on RF (topographic)



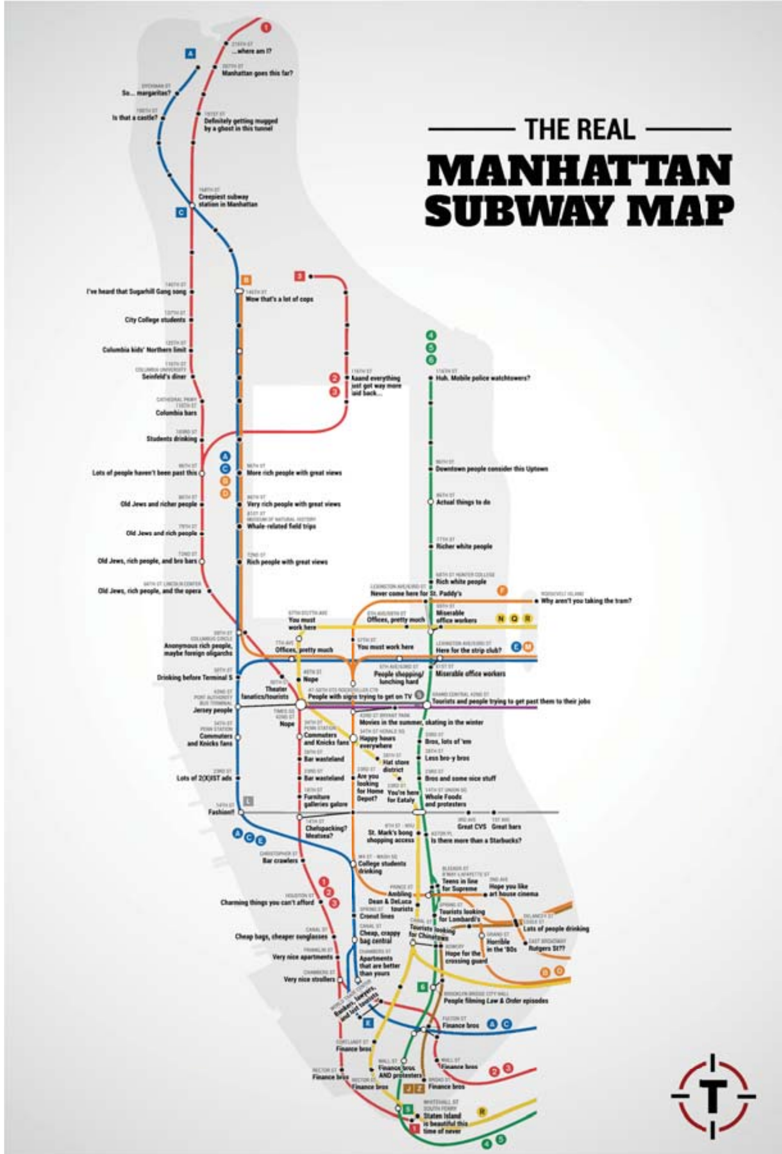
Supervised

Brown et al. (1998) *J Neurosci*
Zhang et al. (1998) *J Neurophysiol*

Spatial representation

1) **metric & topographic** (location-based)

2) **topological** (connectivity-based)



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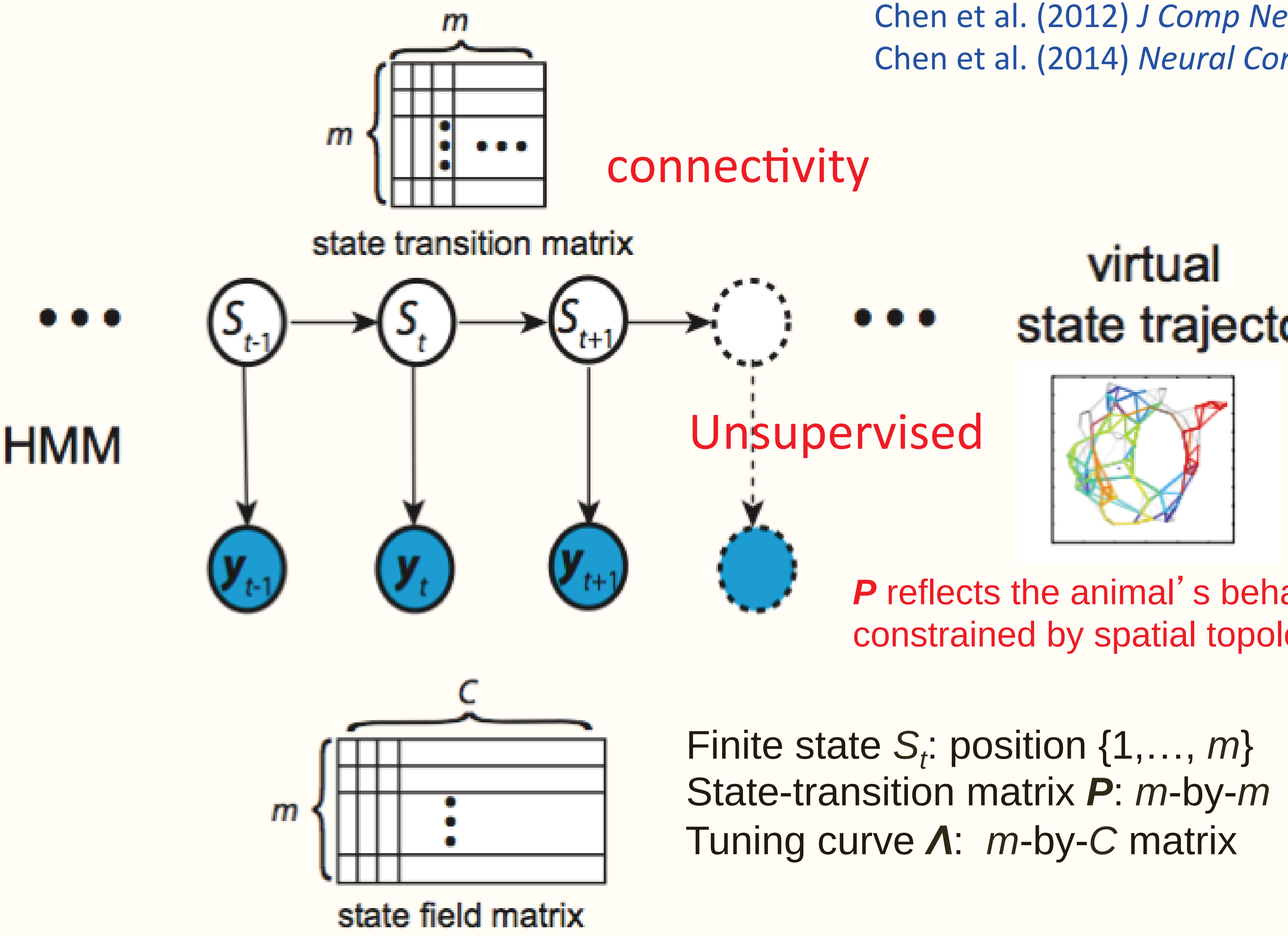
Decode$_{woRF}$: without RF (topological)

Chen et al. (2012) *J Comp Neurosci*
Chen et al. (2014) *Neural Comput*



P reflects the animal's behavior constrained by spatial topology

Finite state S_t: position $\{1,\ldots, m\}$
State-transition matrix $\boldsymbol{P}$: m-by-m
Tuning curve $\boldsymbol{\Lambda}$: m-by-C matrix

$$y_{c,t} \sim Poisson(\lambda_{ci} \, ; \, S_t{=}i)$$

Questions

- In Wake, For HPC downstream structure, how to represent the space with ensemble spikes alone---without *a priori* measurements/storage of the RFs?

- In Sleep, HPC neuronal spike activities are *sparse* (sporadic, low percentage of active neurons)--- how to provide an unbiased read-out assessment of neural codes?

- Two paradigms

behavior → sleep ("meaning first, memory later"), supervised

sleep → behavior ("memory first, meaning later"), unsupervised

Strategy

- Create synthetic sleep-associated spike data: mimic the "sleep code" and assess how does decoding ($\text{Decode}_{\text{wRF}}$ vs. $\text{Decode}_{\text{woRF}}$) performance depend on --- sample size, episode length, number of active neurons (15-20%), lower spike rate ("thinning"), temporal bin size, place RF size ....

- Quantitative assessment

  i) median decoding error (representation)--- 2D environment

  ii) weighted correlation *R* and Z-score (detection reliability)– 1D environment

$$Z = \frac{R - \text{mean of } R_{\text{shuffle}}}{\text{SD of } R_{\text{shuffle}}},$$

- Experimental sleep data (criterion ii)

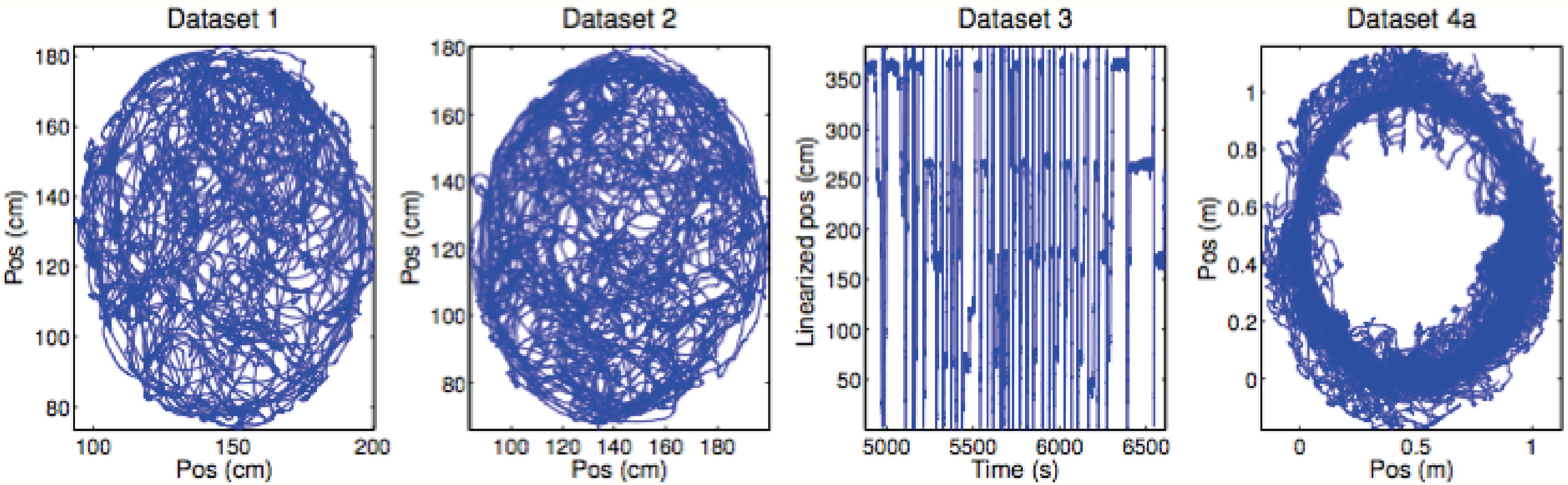
Chen et al. *Neural Comp.* 2014
Linderman et al. *J. Neurosci Methods*, 2016
Chen et al. *Scientific Reports*, 2016

Datasets

Hector Penagos (MIT)

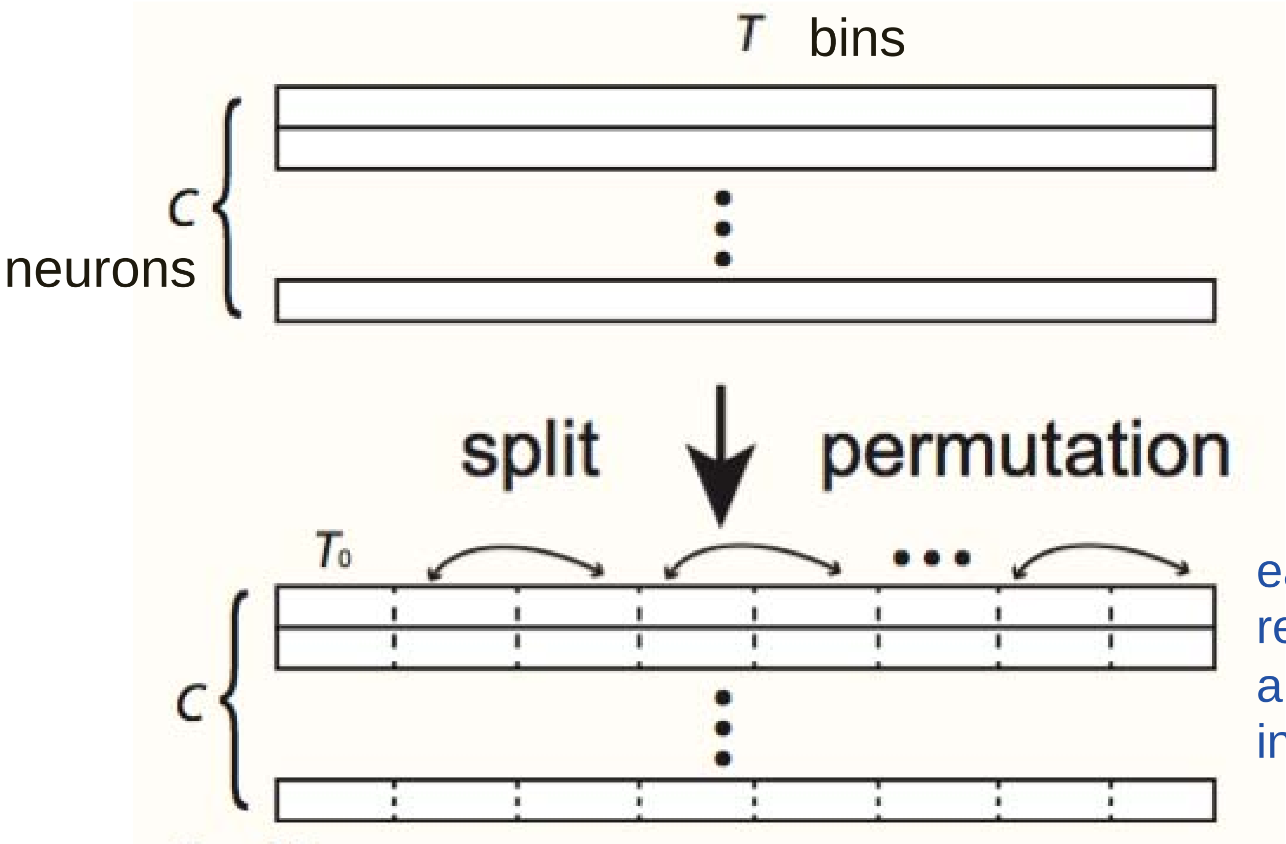
A. Grosmark (NYU/Columbia)

Dataset	# Place cells	Rate (Hz) (mean±SEM)	Recording (run) time (min)	Environment
1	49	1.48±0.45	24.3 (9.8)	open field
2	37	1.32±0.13	22.9 (12.3)	open field
3	50	0.64±0.07	28.9 (10.2)	circular track
4a	77	1.11±0.08	44.6 (25.4)	circular track
4b	77	0.66±0.05	480 (N/A)	rest/sleep box

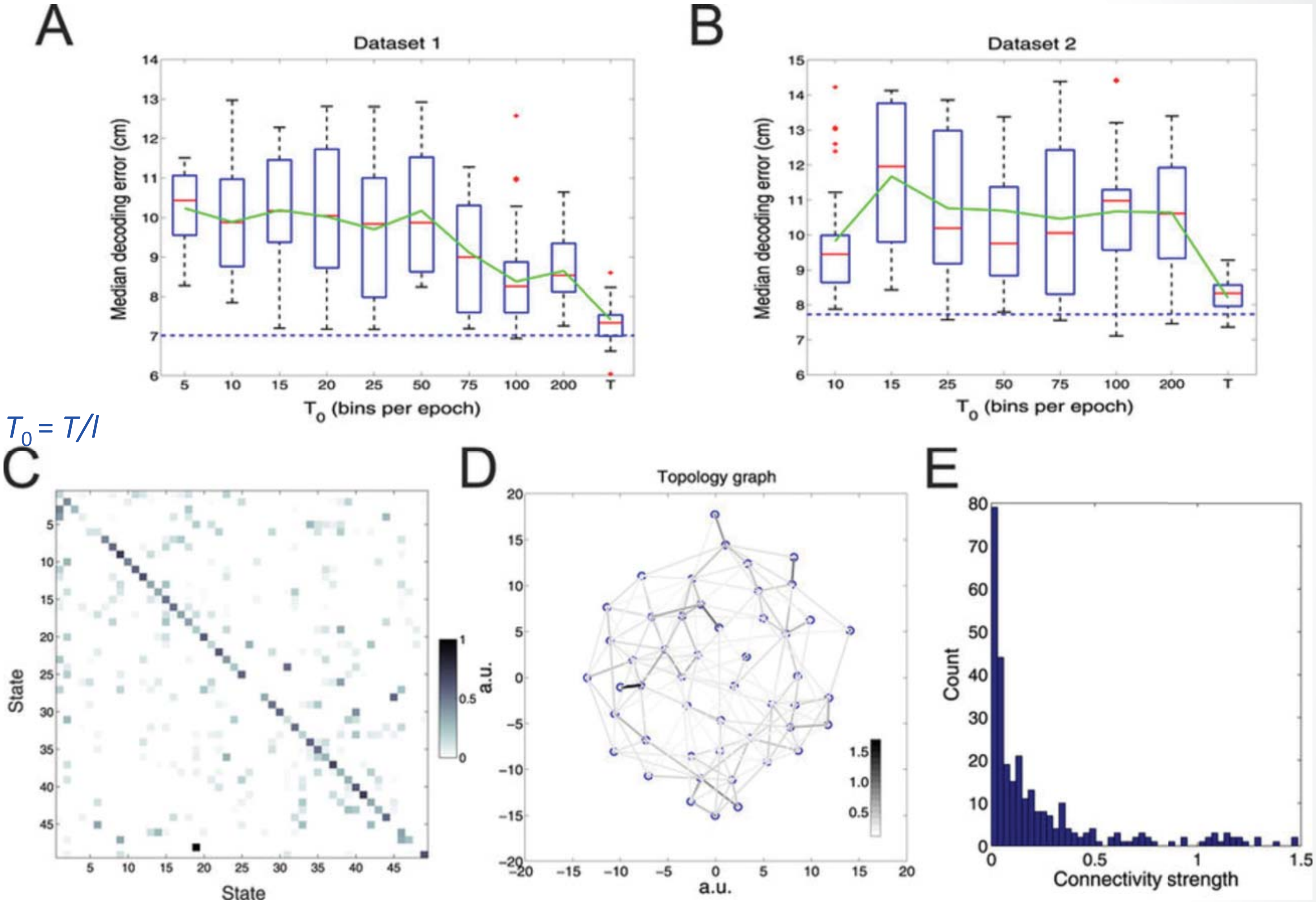


Synthetic sleep-like spike data
(derived from run-associated spike data)

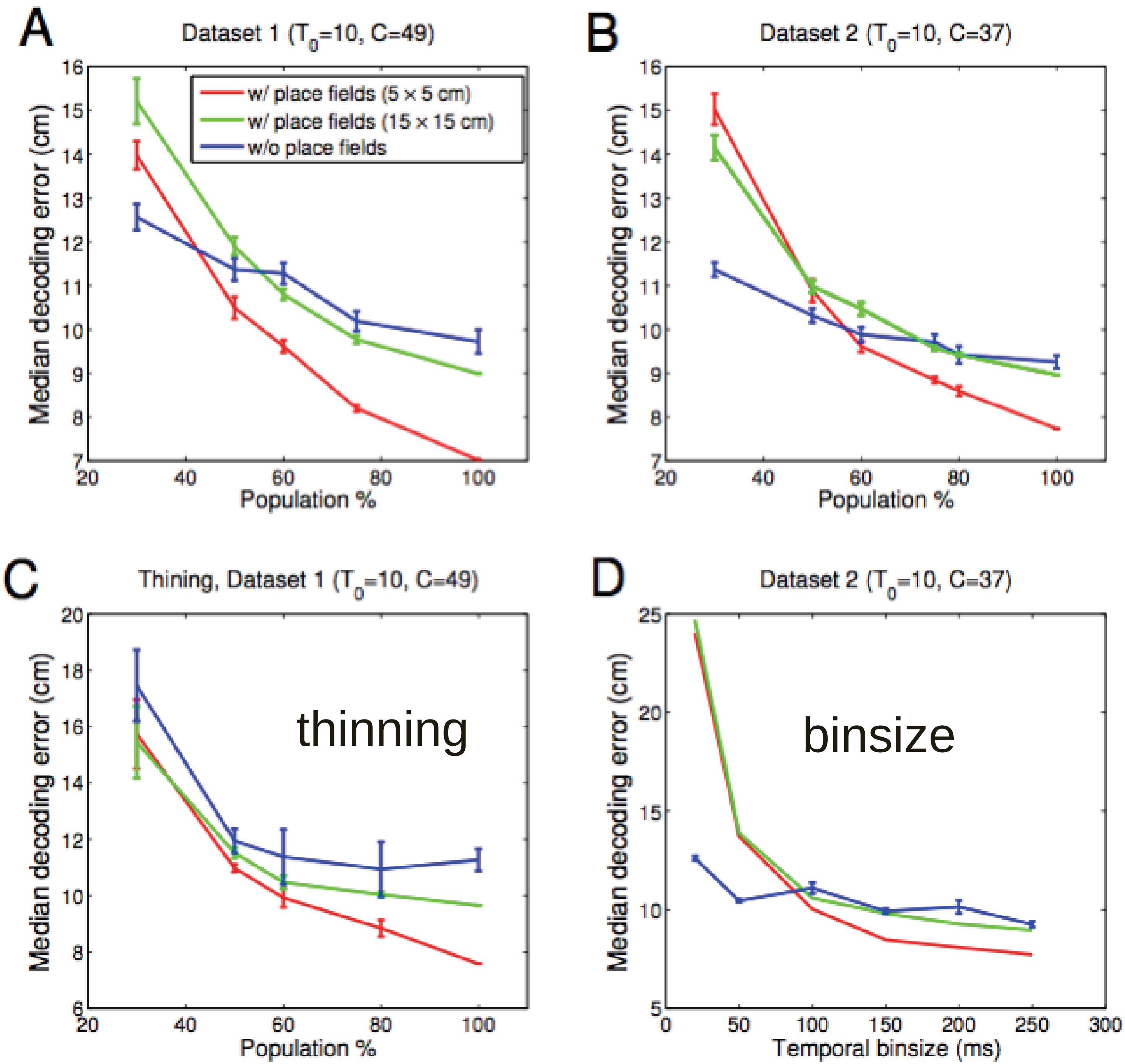
- Split, time shuffle, direction shift (remove long-range temporal dependence, preserve short-range dependence)

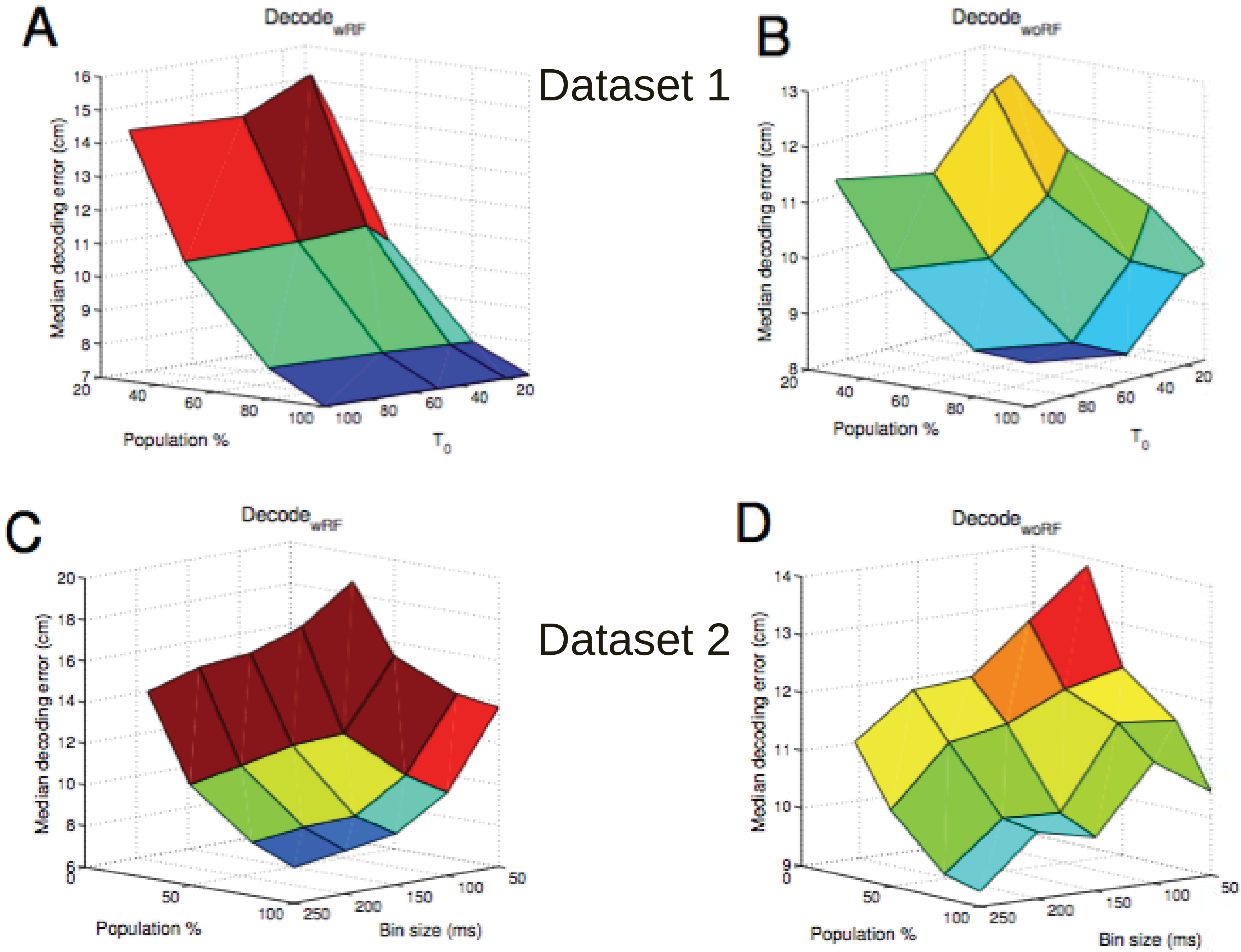


each epoch
represents
a snapshot
in sleep episodes


A
Dataset 1
Median decoding error (cm)
T0 (bins per epoch)
B
Dataset 2
Median decoding error (cm)
T0 (bins per epoch)
C
State
State
D
Topology graph
a.u.
a.u.
E
Count
Connectivity strength

$T_0 = T/l$


A
Dataset 1 (T_0=10, C=49)
w/ place fields (5 × 5 cm)
w/ place fields (15 × 15 cm)
w/o place fields
Median decoding error (cm)
Population %
B
Dataset 2 (T_0=10, C=37)
Median decoding error (cm)
Population %
C
Thining, Dataset 1 (T_0=10, C=49)
thinning
Median decoding error (cm)
Population %
D
Dataset 2 (T_0=10, C=37)
binsize
Median decoding error (cm)
Temporal binsize (ms)

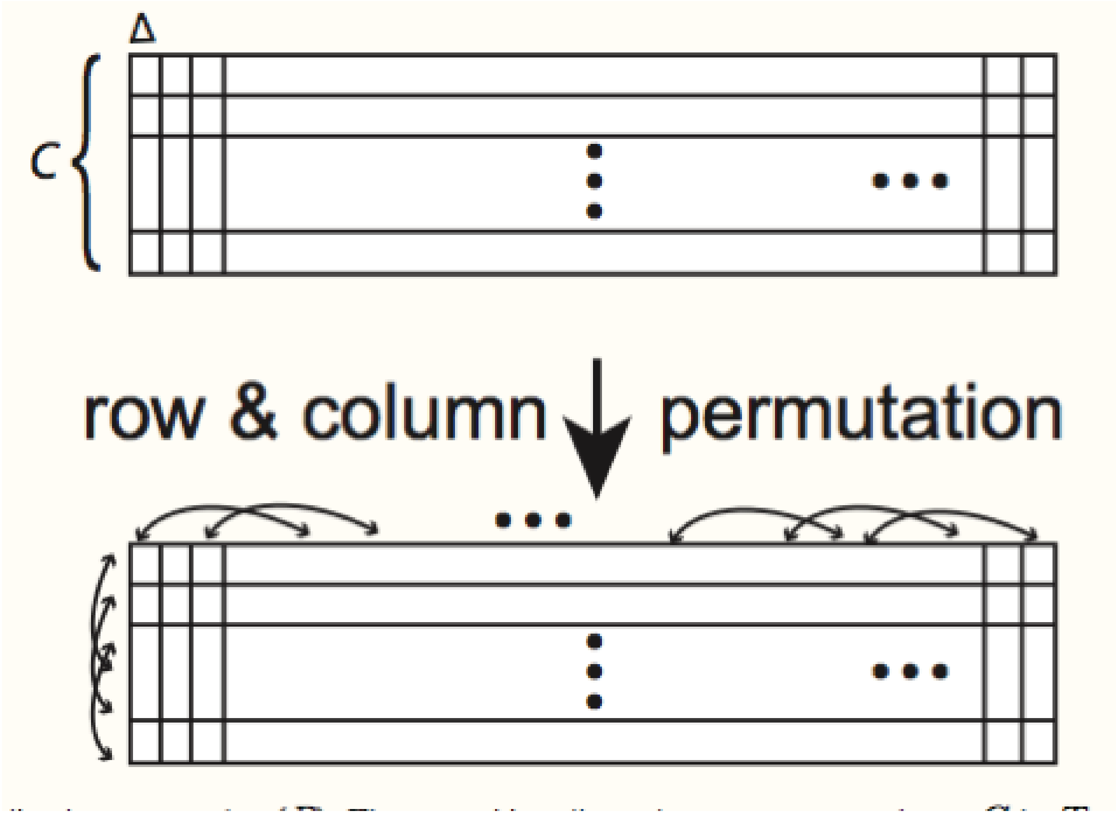


Dataset 1

Dataset 2

Test detection power

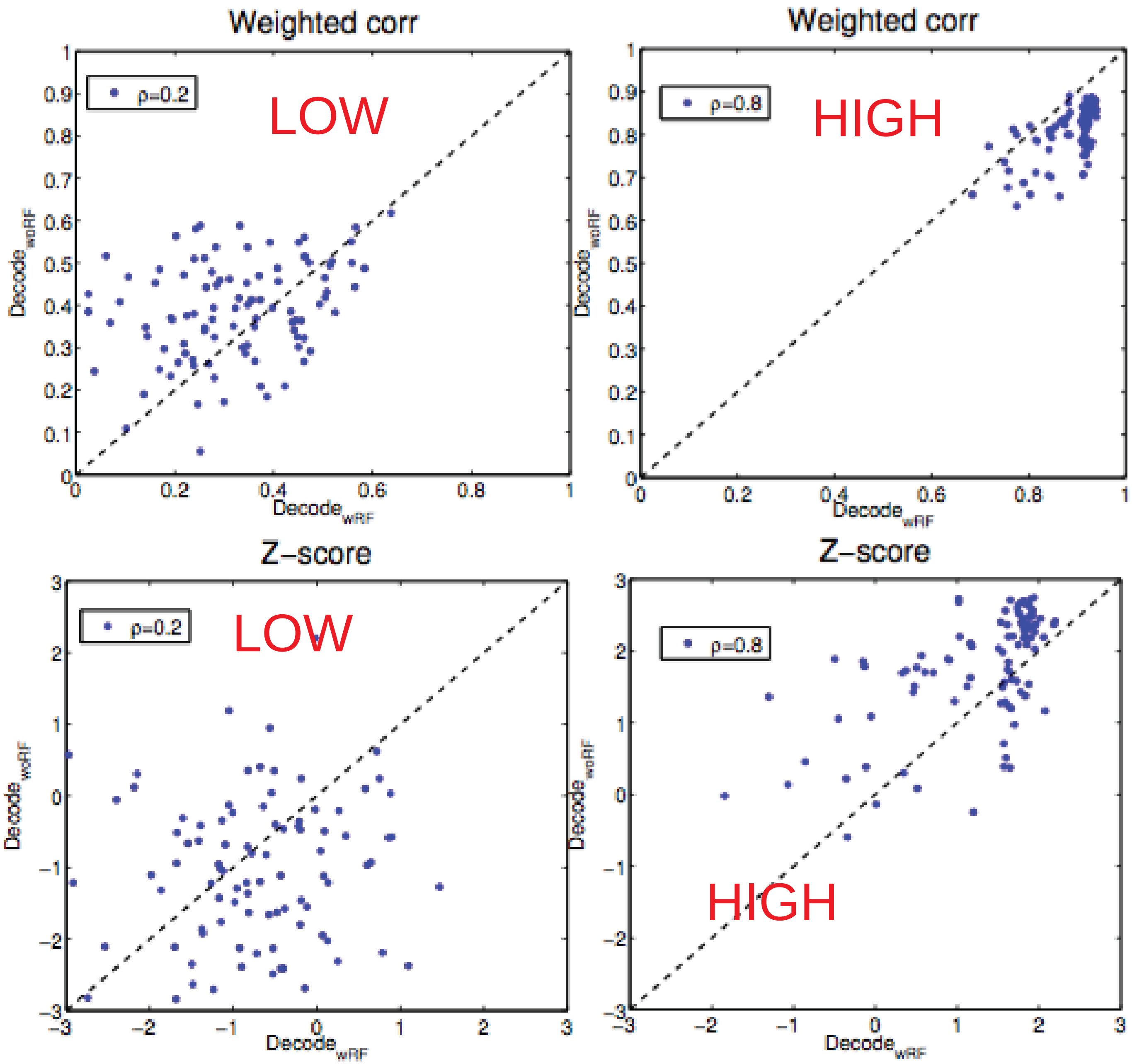
- Significance testing via randomly shuffled data (1000 samples)



Cell shuffling

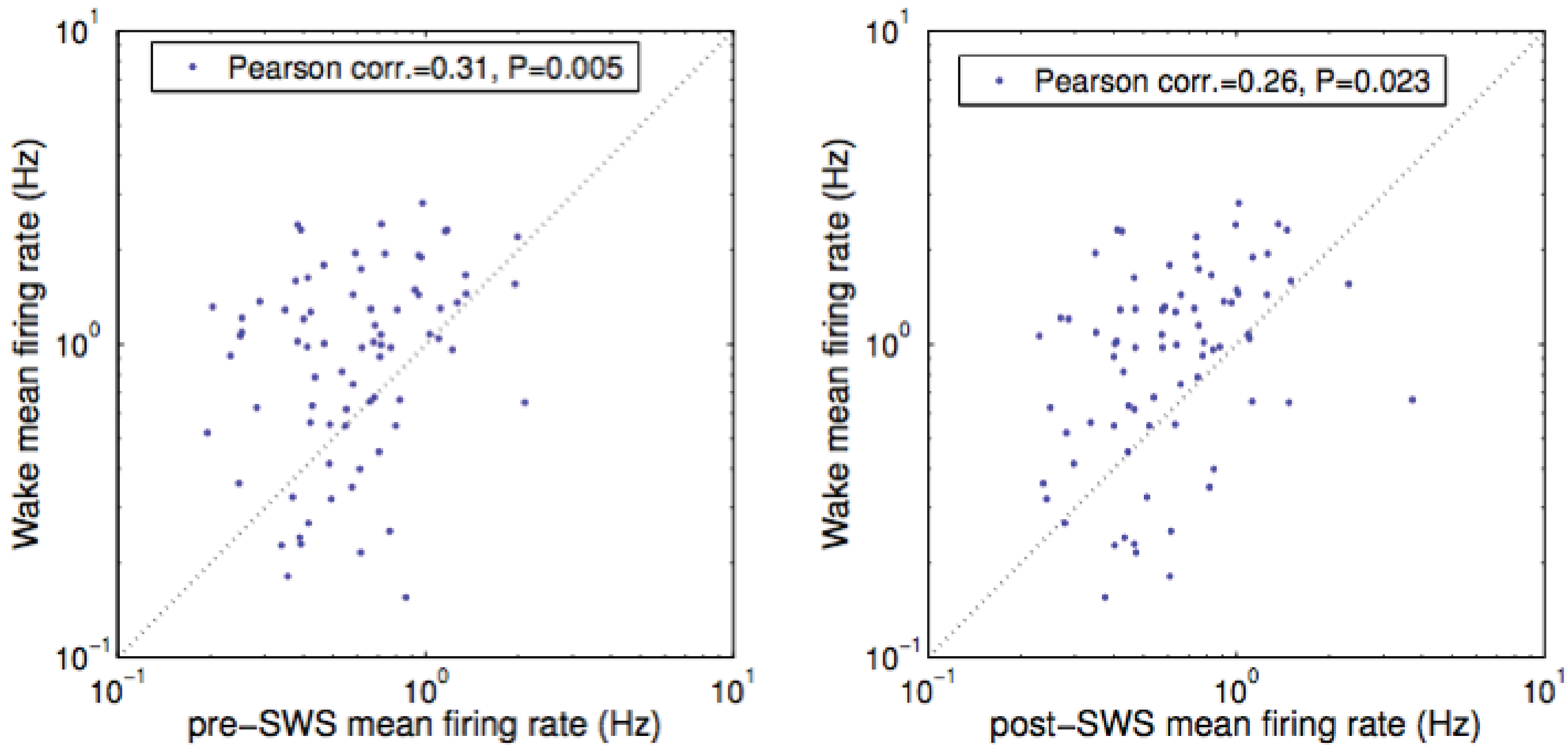
Temporal shuffling

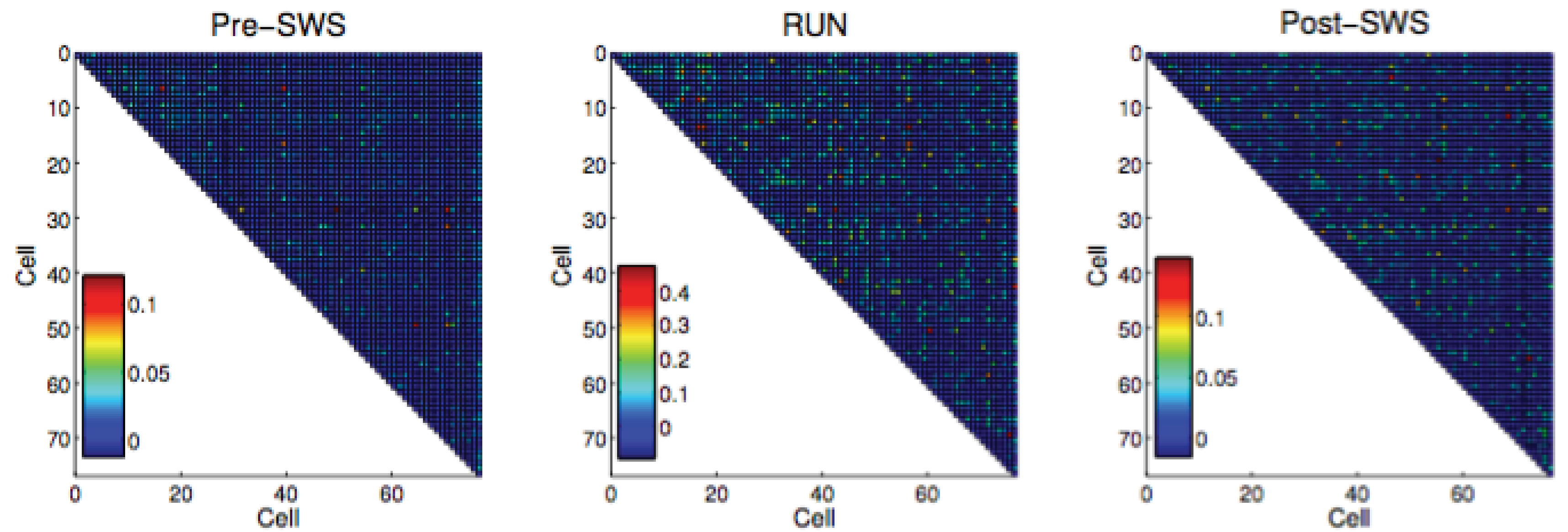
ρ: active cell ratio (Dataset 3)



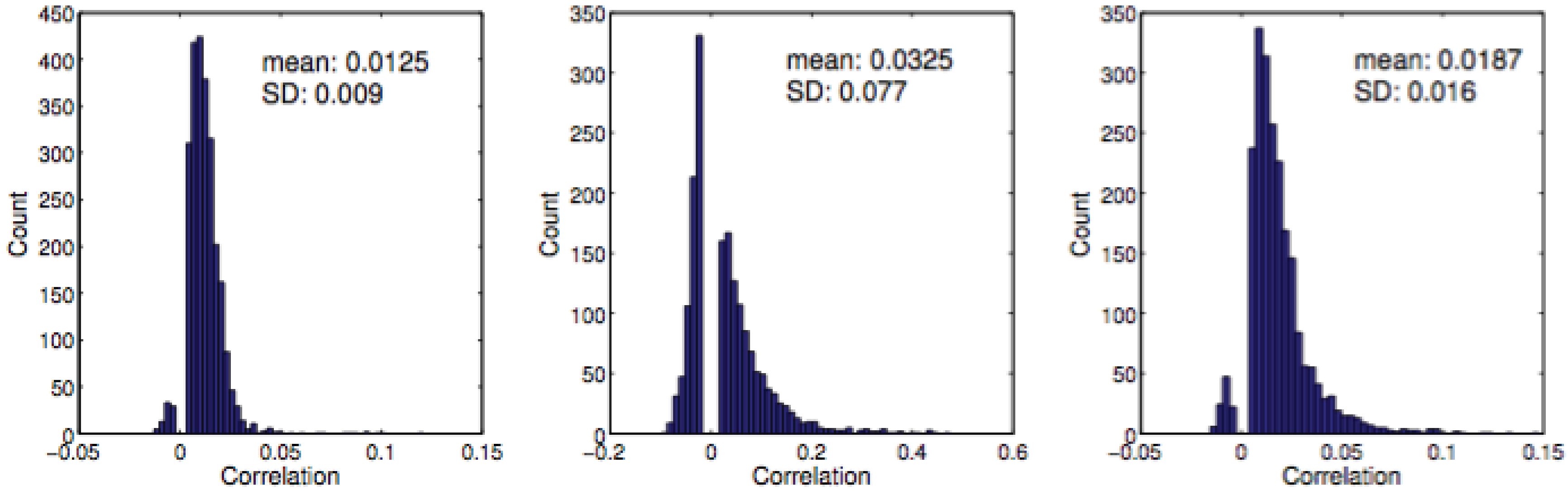
Pre-SWS vs. Post-SWS

- Sleep firing rate correlates with Wake firing rate (Datasets 4a & 4b)
- No significant difference pre-SWS vs. post-SWS firing rate

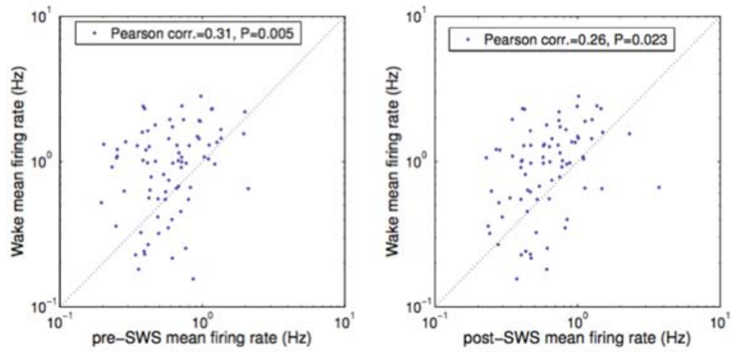




Pairwise Pearson's correlation



Pre vs. Post-SWS



***ρ* (active cell ratio):** (P = 0.31, rank-sum test)

pre-SWS: $\rho = 0.175 \pm 0.003$, maximum 0.45, median 0.16

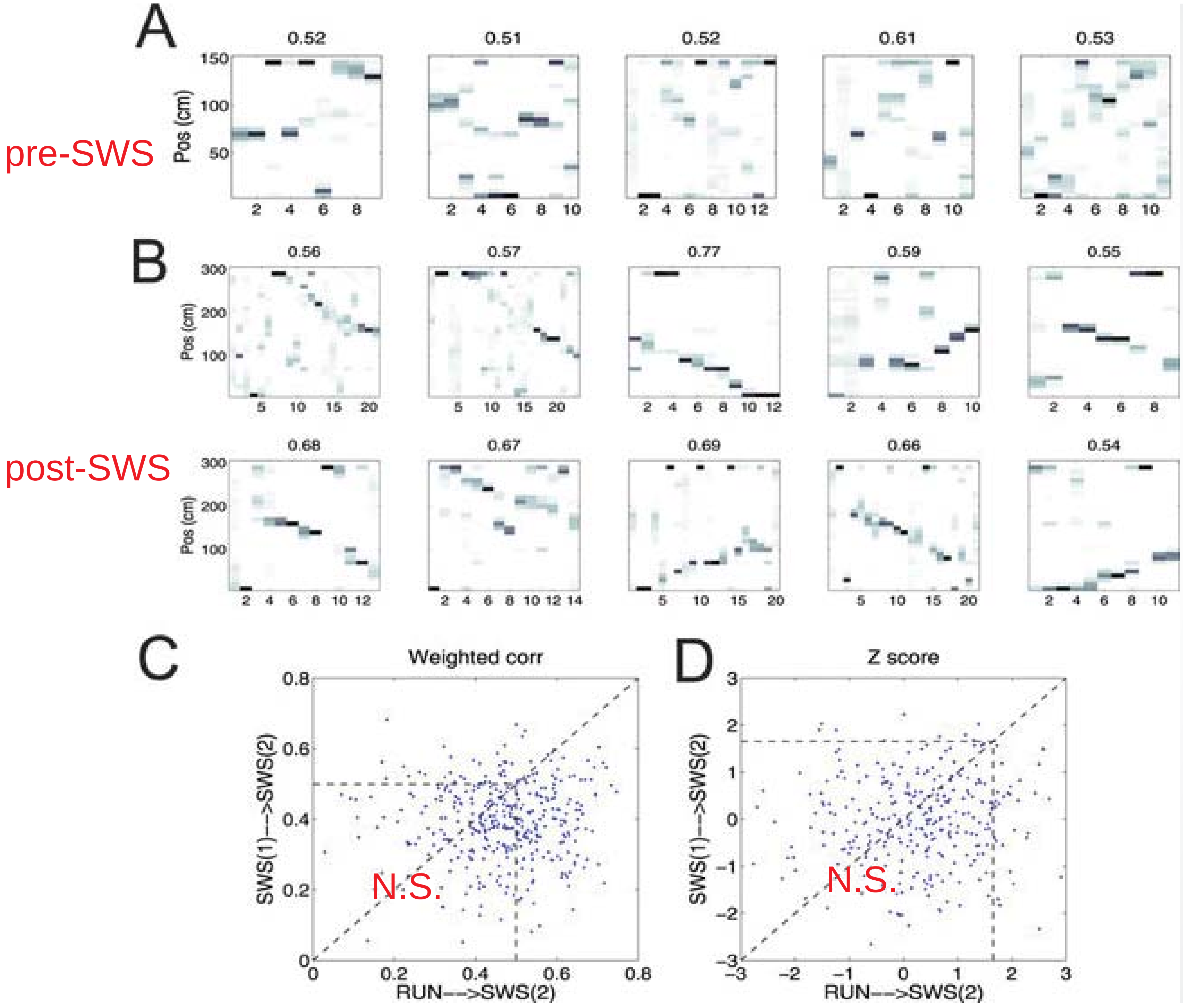
post-SWS: $\rho = 0.178 \pm 0.003$, maximum 0.53, median 0.16

Δ = 20 ms

the number of bins per epoch (P = 0.006, rank-sum test)

pre-SWS: $T_0 = 12.7 \pm 0.3$ bpe

post-SWS: $T_0 = 11.9 \pm 0.2$ bpe

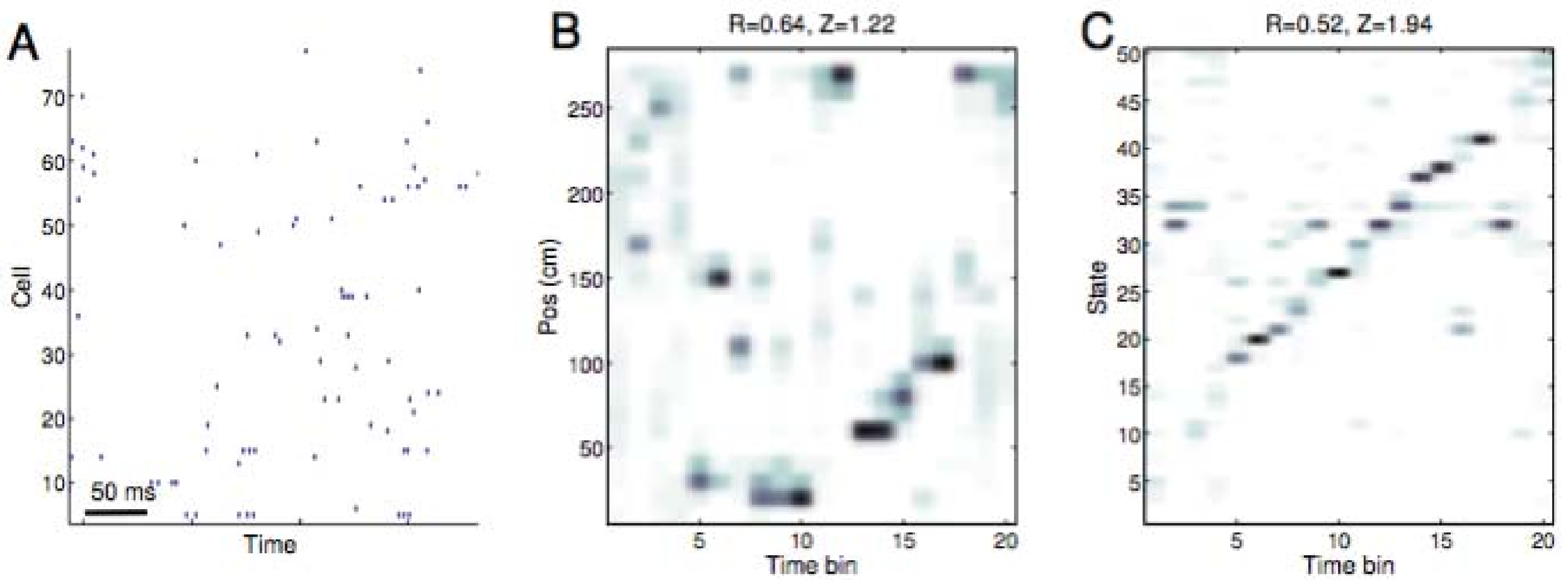

A
pre-SWS
0.52
0.51
0.52
0.61
0.53
Pos (cm)
B
0.56
0.57
0.77
0.59
0.55
Pos (cm)
post-SWS
0.68
0.67
0.69
0.66
0.54
Pos (cm)
C
Weighted corr
SWS(1)-->SWS(2)
RUN-->SWS(2)
N.S.
D
Z score
SWS(1)-->SWS(2)
RUN-->SWS(2)
N.S.

Decode$_{wRF}$ vs Decode$_{woRF}$

Example of post-SWS hippocampal ensemble spikes

- Decode$_{wRF}$: spatial resolution is limited by RF size; linear fit discontinuity
- Decode$_{woRF}$: spatial resolution is adaptive; lower R but higher Z-score

consistent with simulations



Take home message

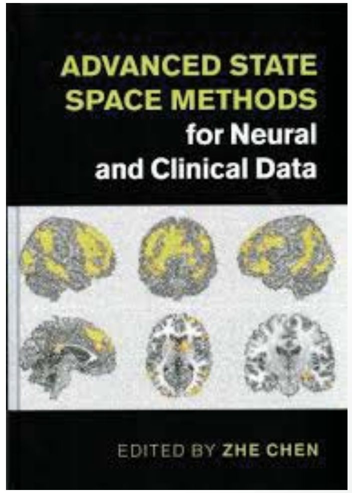
- Unsupervised learning approach can discover latent structures of ensemble spike activity (no RF model is required).
- number of active hippocampal pyramidal neurons are critical for reliable representation of the space as well as for detection of spatiotemporal reactivated patterns.
- NEW paradigm (“*memory or structure first, meaning later*”) provides an unbiased approach to discover hidden meaning and structure in brain activity, perhaps reflecting other non-spatial hippocampal memories.

NIH National Institute of Neurological Disorders and Stroke

- NSF-CRCNS achievements (10/2013-present)
- **Partnership**: Matt Wilson (MIT, Co-PI),

  Gyuri Buzsaki (NYU), Howard Eichenbaum (BU), Sridevi Sarma (JHU)

- 12 Journal articles in press or accepted (*Neural Computat. x 2, J. Neurophysiol., Cell, Comput. Intel. Neurosci., IEEE Trans. PAMI x 2, IEEE Signal Proc. Mag., Front. Neural Circuits, J. Neurosci. Methods, Scientific Reports*)
- 1 book & 3 book chapters



- Two computer software packages online

  (github.com)