Spike Train Analysis II:

correlation analysis and surrogate methods

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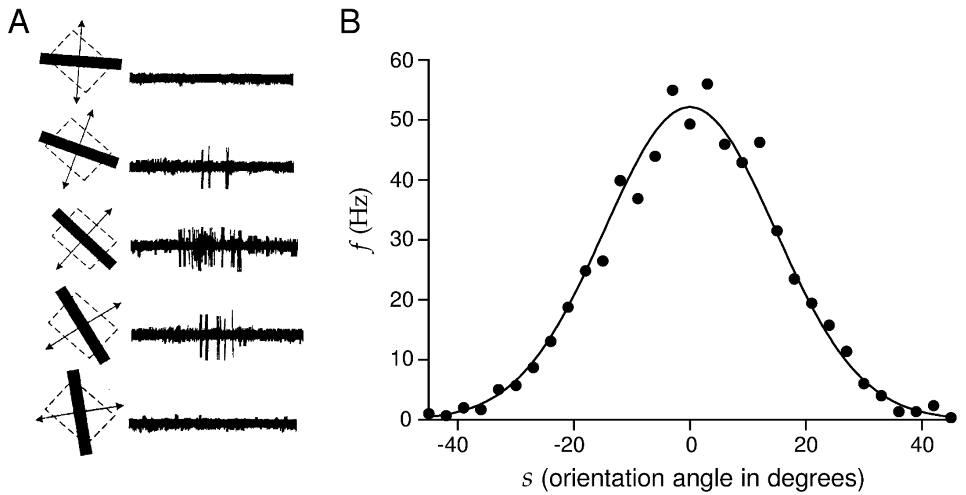
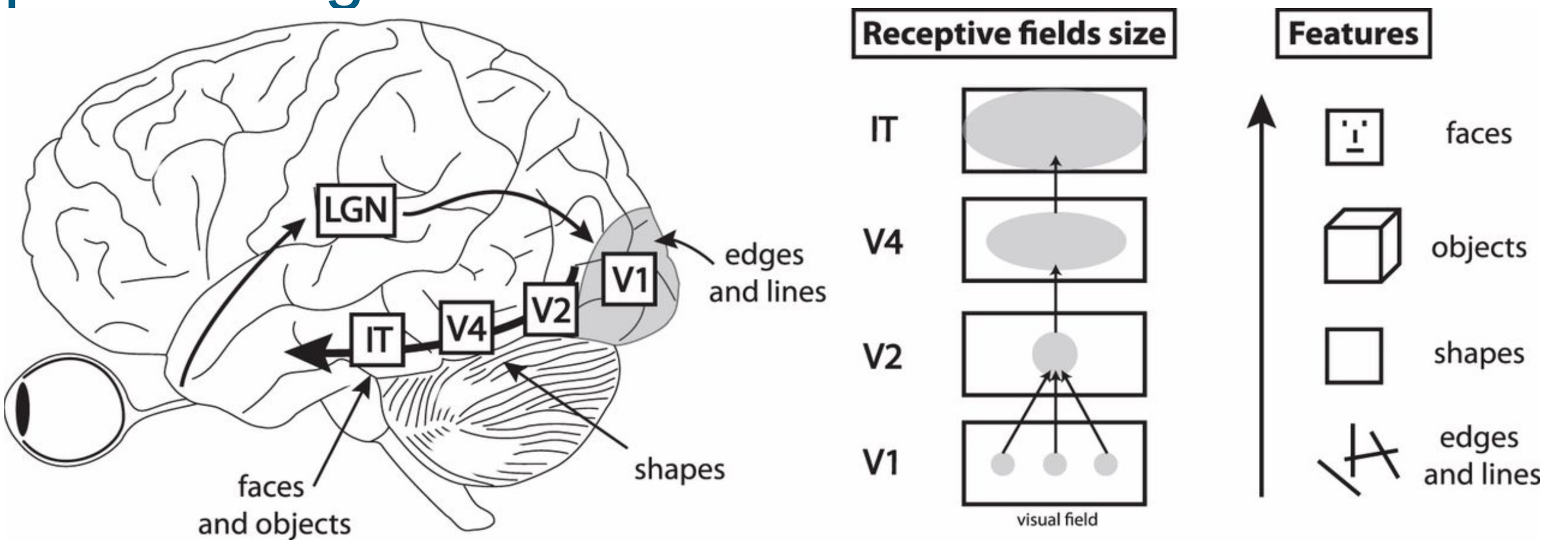
Recap | response to visual stimulus

- Neurons in the primary visual cortex have...
  - Receptive field: a particular region of the visual field in which a stimulus triggers the firing of that neuron.
  - Orientation preference: a particular orientation of stimulus to which that neuron respond strongly



From: Dayan and Abbott (2008)

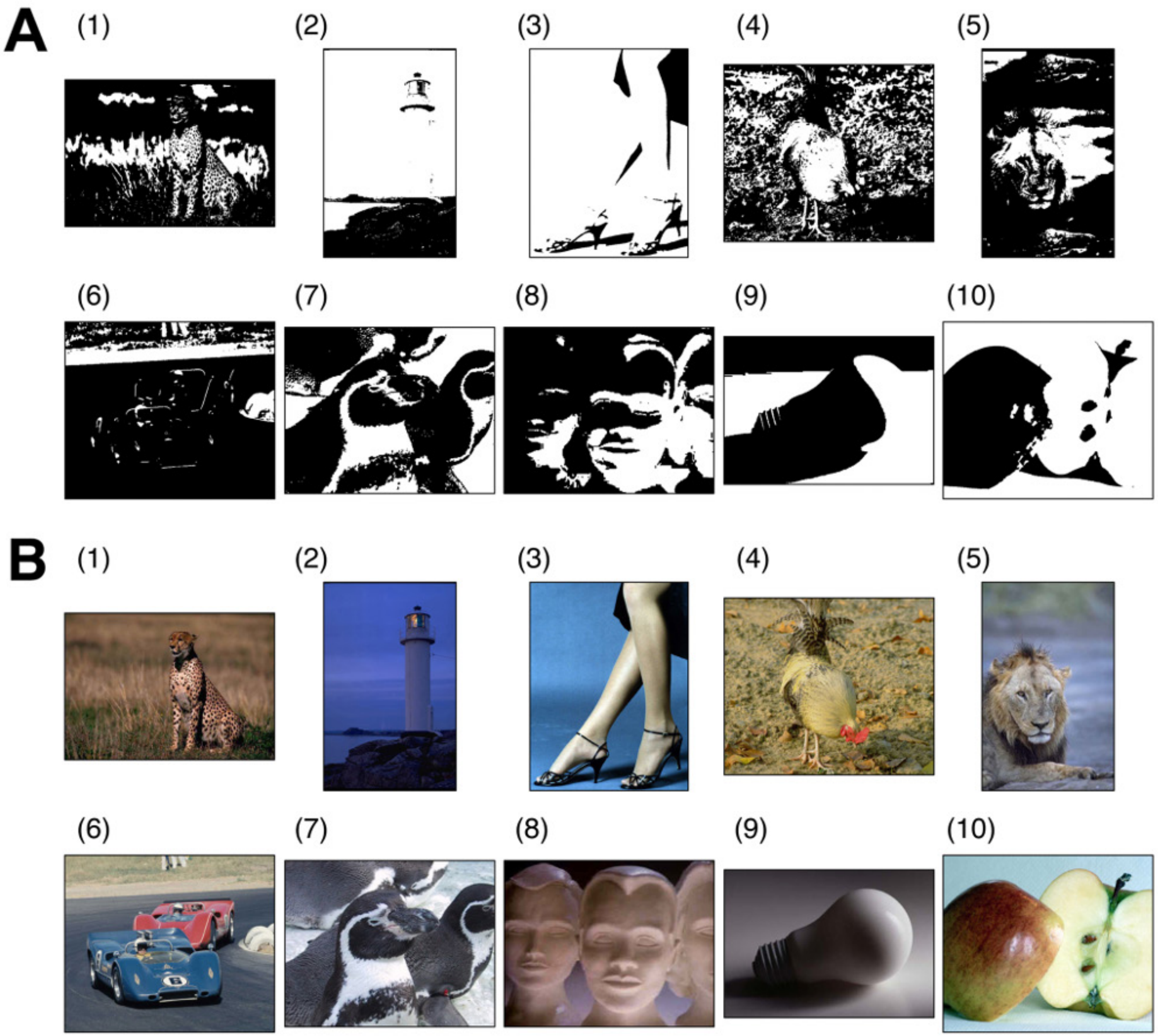
Introduction | hierarchical visual processing



From: Mannasi et al. (2005) J Vis 13:1-10

- As processing proceeds through the hierarchy…
  - Receptive field size gets larger
  - Represented feature gets more complex

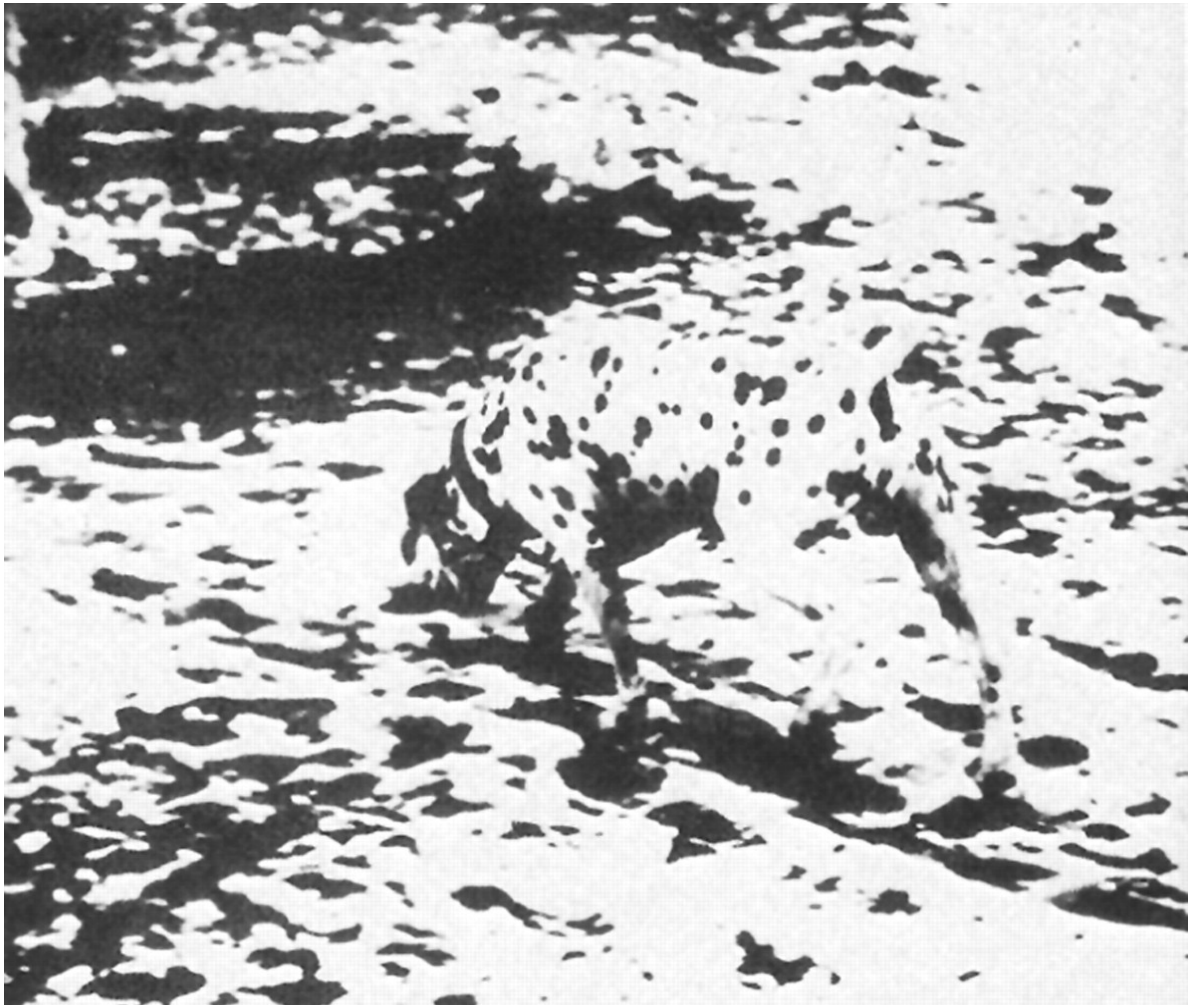
Demo



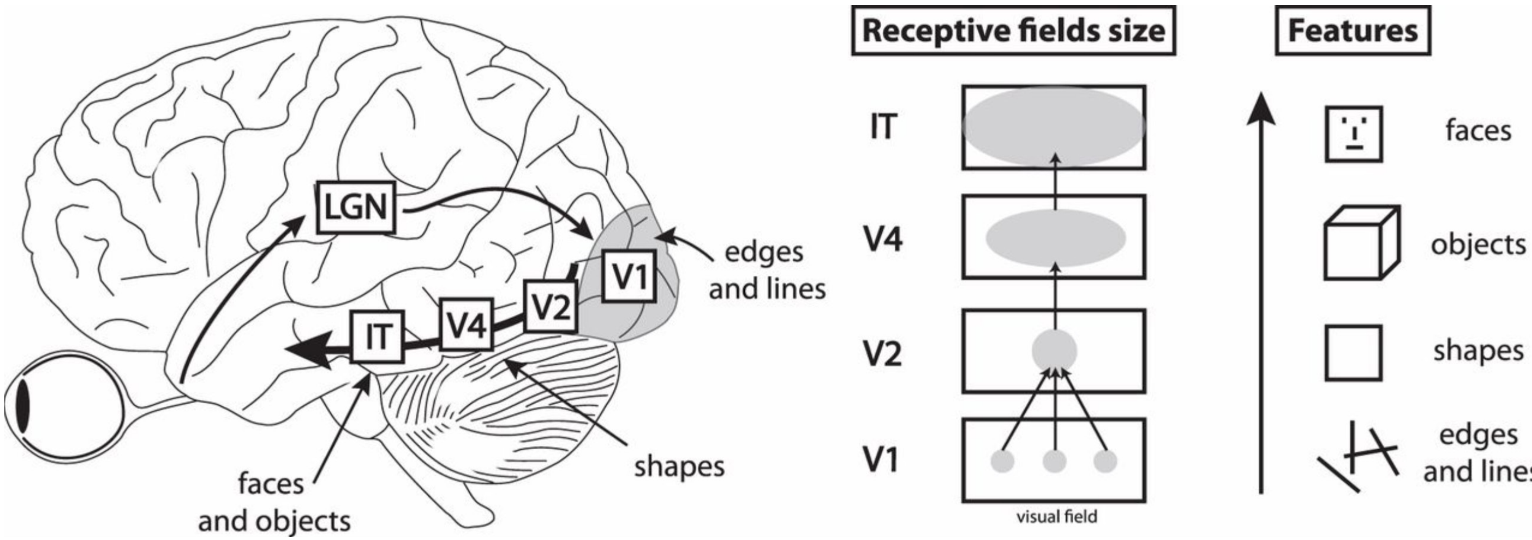
From: Murata et al. (2014) PLoS ONE 9:e115658

Demo

Demo



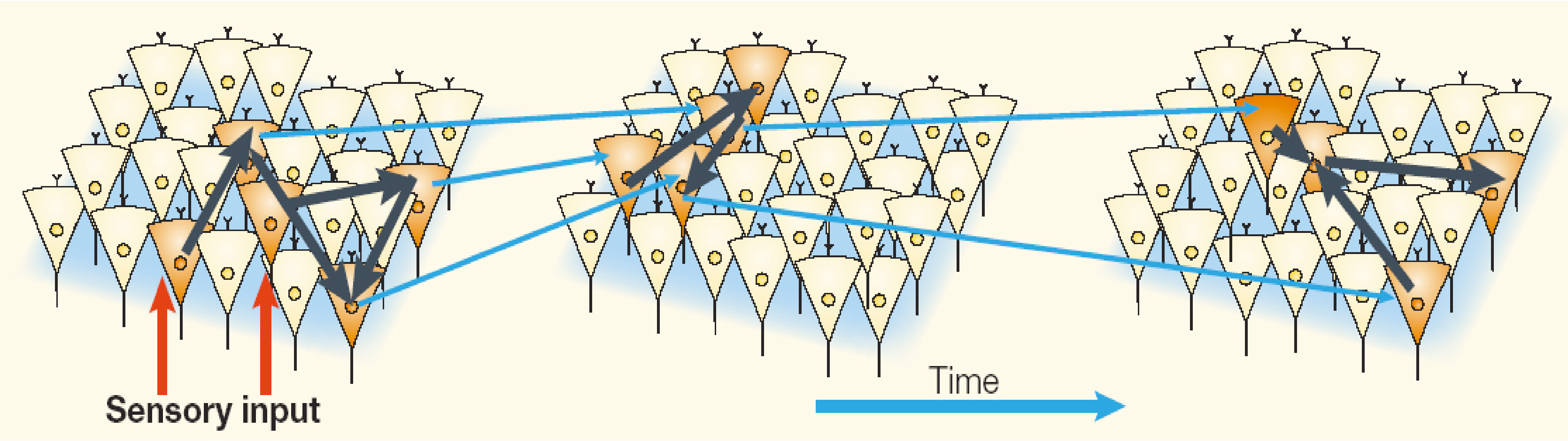
Motivation | question



From: Mannasi et al. (2005) J Vis 13:1-10

- In the demo, you saw exactly the same image before and after you were aware of the dog.
- What difference in the brain activity makes you **aware** or **not aware** of the dog?

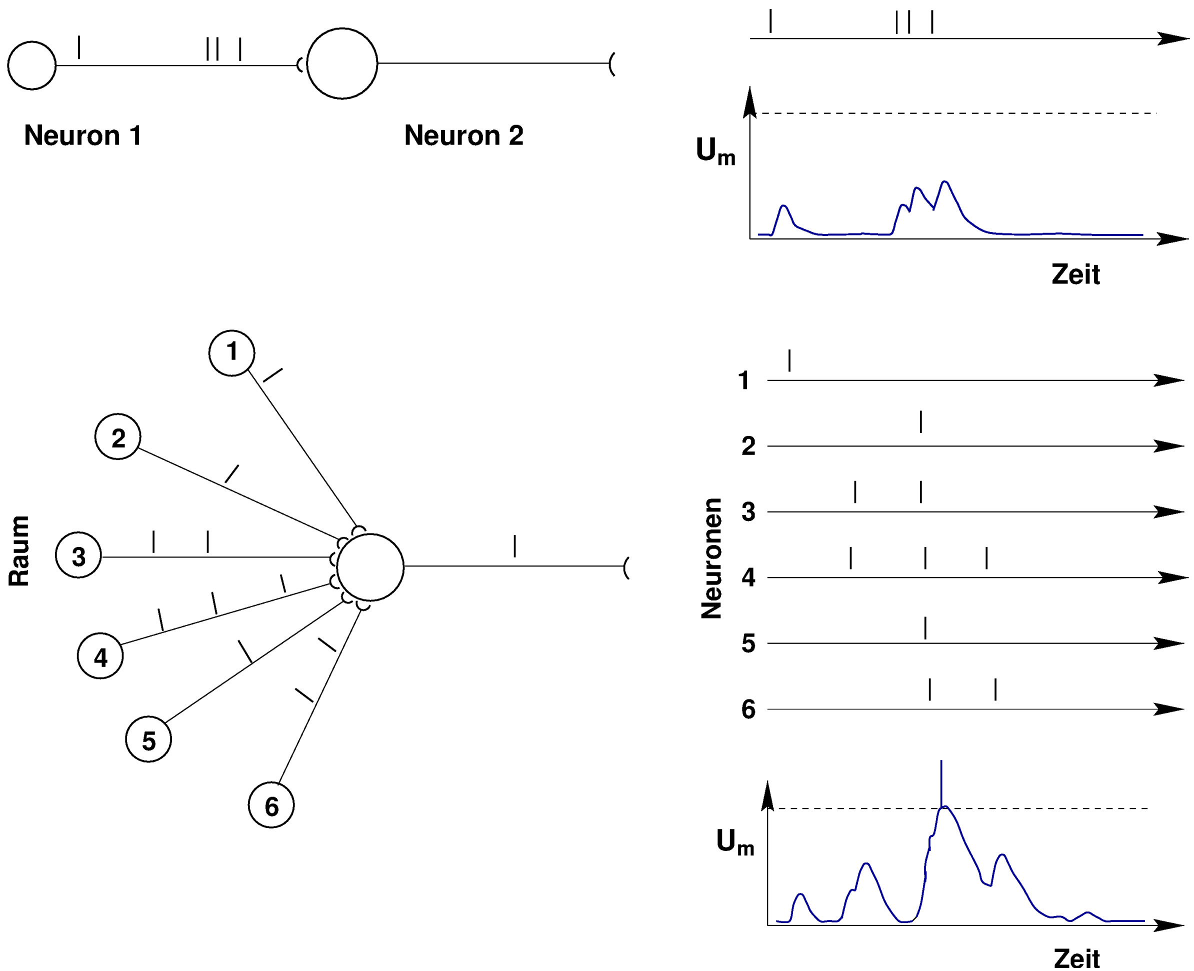
Motivation | underlying neuronal activity



From: Harris (2005) Nat Rev Neurosci 6:399-407

- Processing by interaction of neurons
- Activity propagates across processing stages

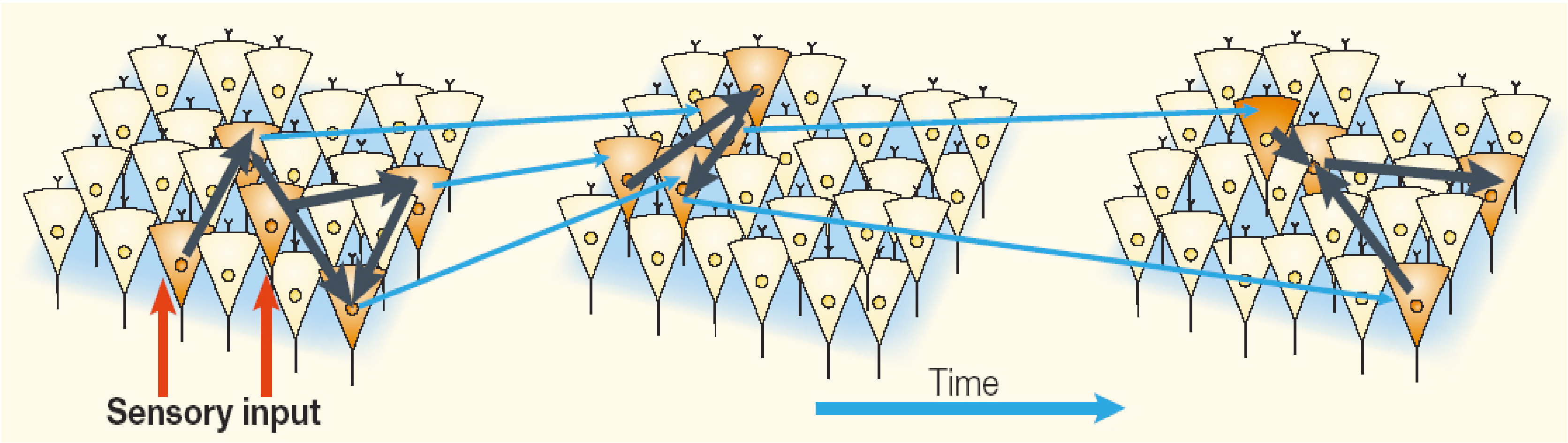
Motivation | what makes a neuron fire?



- Cortical neuron: single EPSP far from threshold
- Synchronous input effective in generating output spikes

Abeles (1982) Isr J Med Sci 18: 83--92; Abeles (1991) Corticonics, Cambridge Univ Press; Koenig et al (1996) TINS 19: 130--137; Salinas & Sejnowski (2000) JNS 20:6193-6209; etc.

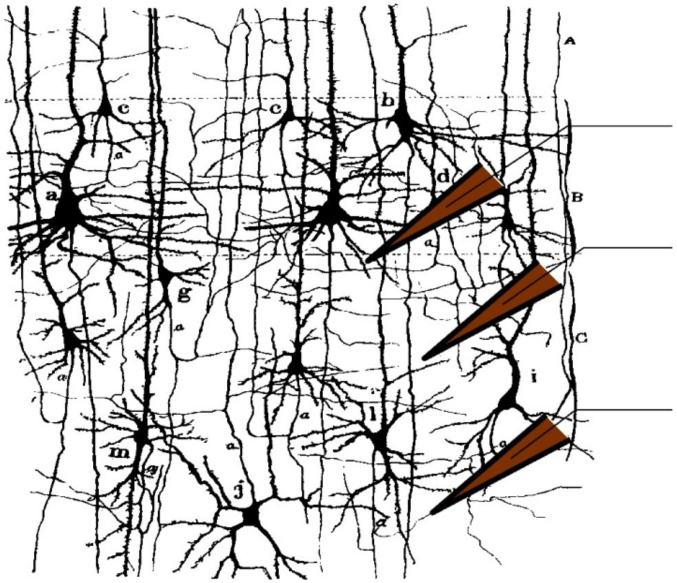
Motivation | binding-by-synchrony hypothesis

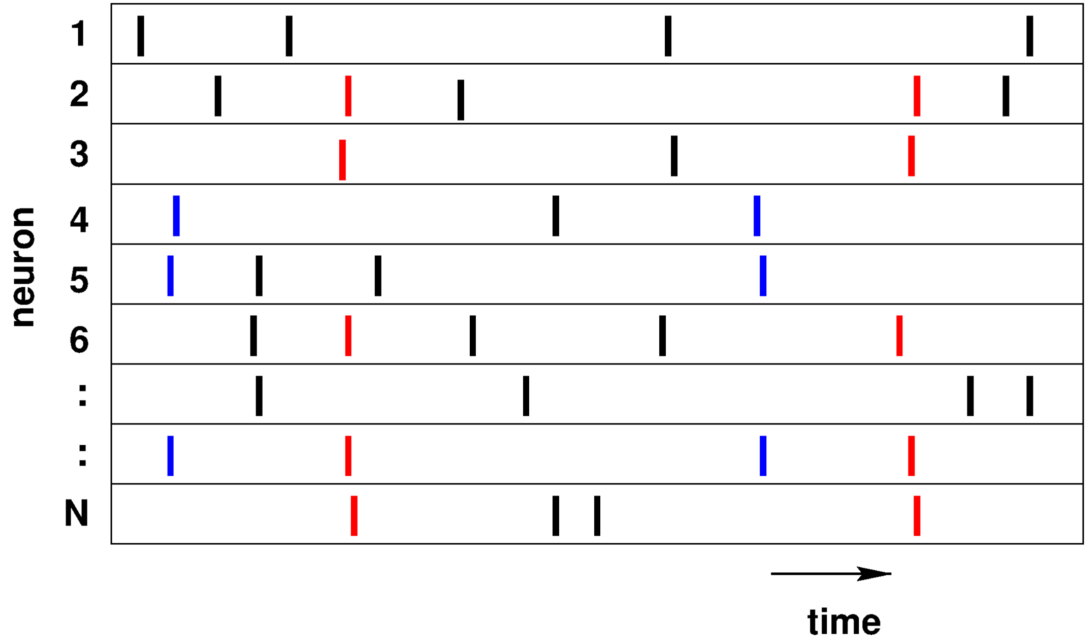


From: Harris (2005) Nat Rev Neurosci 6:399-407

- Cell assemblies act as building blocks for information processing, by firing spikes synchronously, in order to propagate their activity stably across processing stages

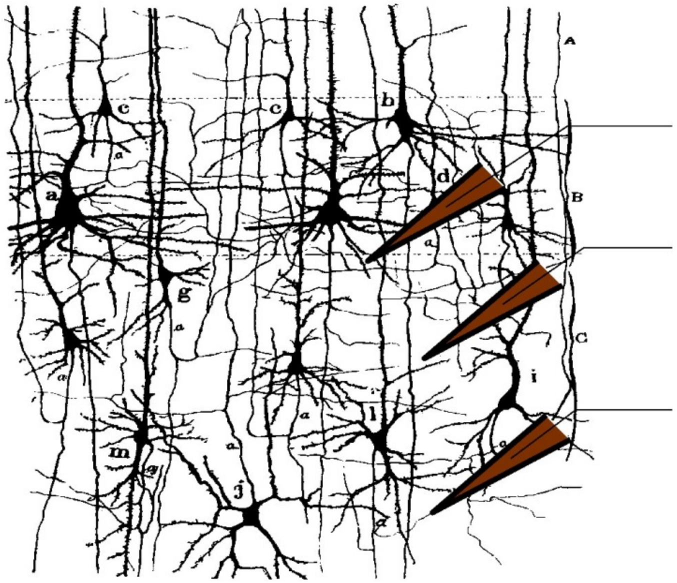
Motivation | binding-by-synchrony hypothesis

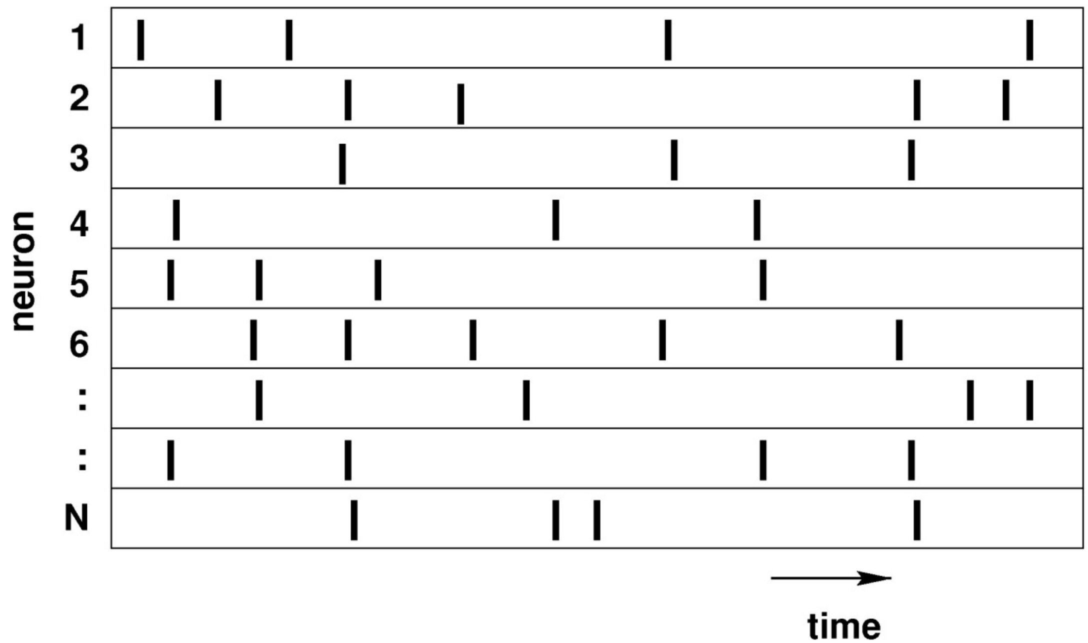




- Cell assemblies act as building blocks for information processing, by firing spikes synchronously, in order to propagate their activity stably across processing stages
- Assembly membership is expressed by coordinated spiking activity

Motivation | goal





- Identify coordinated spiking activity in spike trains of multiple neurons

  → **cross-correlation analysis**

Outline

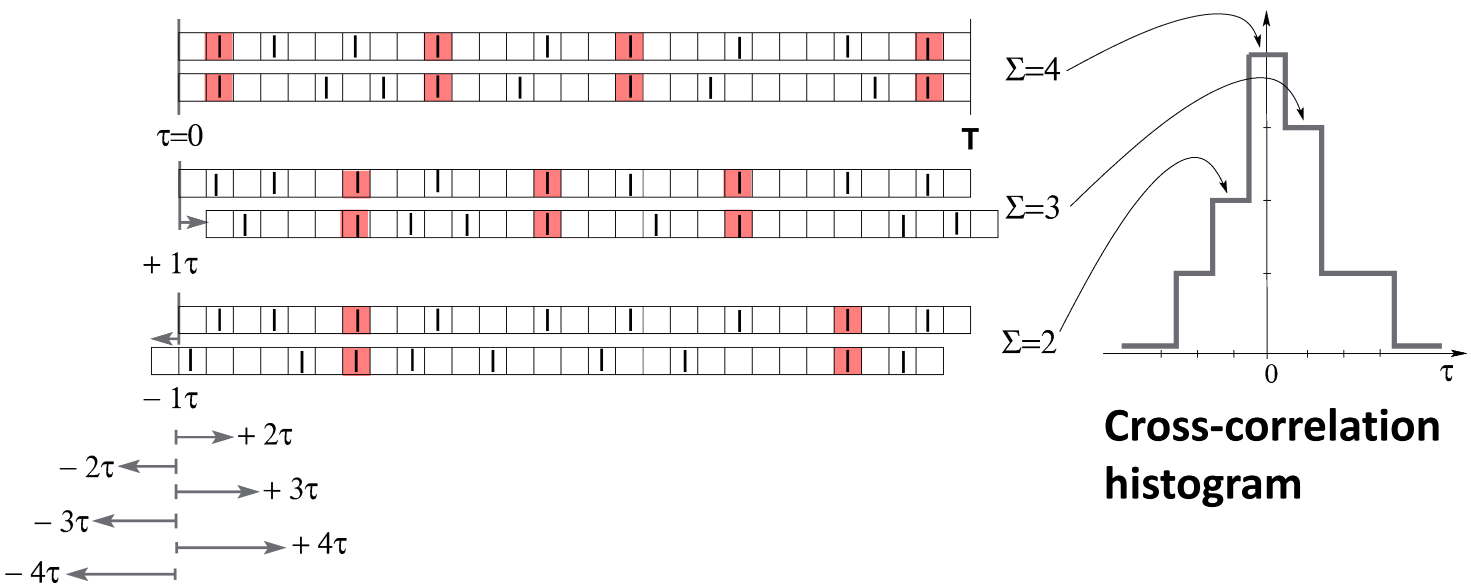
- **Methods**
  - Cross-correlation analysis
  - Significance test
- **Applications**
  - Relation to gestalt perception
    - Cat V1 data (response to visual edges)
    - Monkey MT data (response to visual movement)
  - Relation to network architecture
    - Rat somatosensory cortex (anesthesia)
    - Human neocortex (during sleep)

Methods | cross-correlation histogram

- The **cross-correlation function** is a measure of similarity between two time series $s_1(t)$ and $s_2(t)$ defined as:

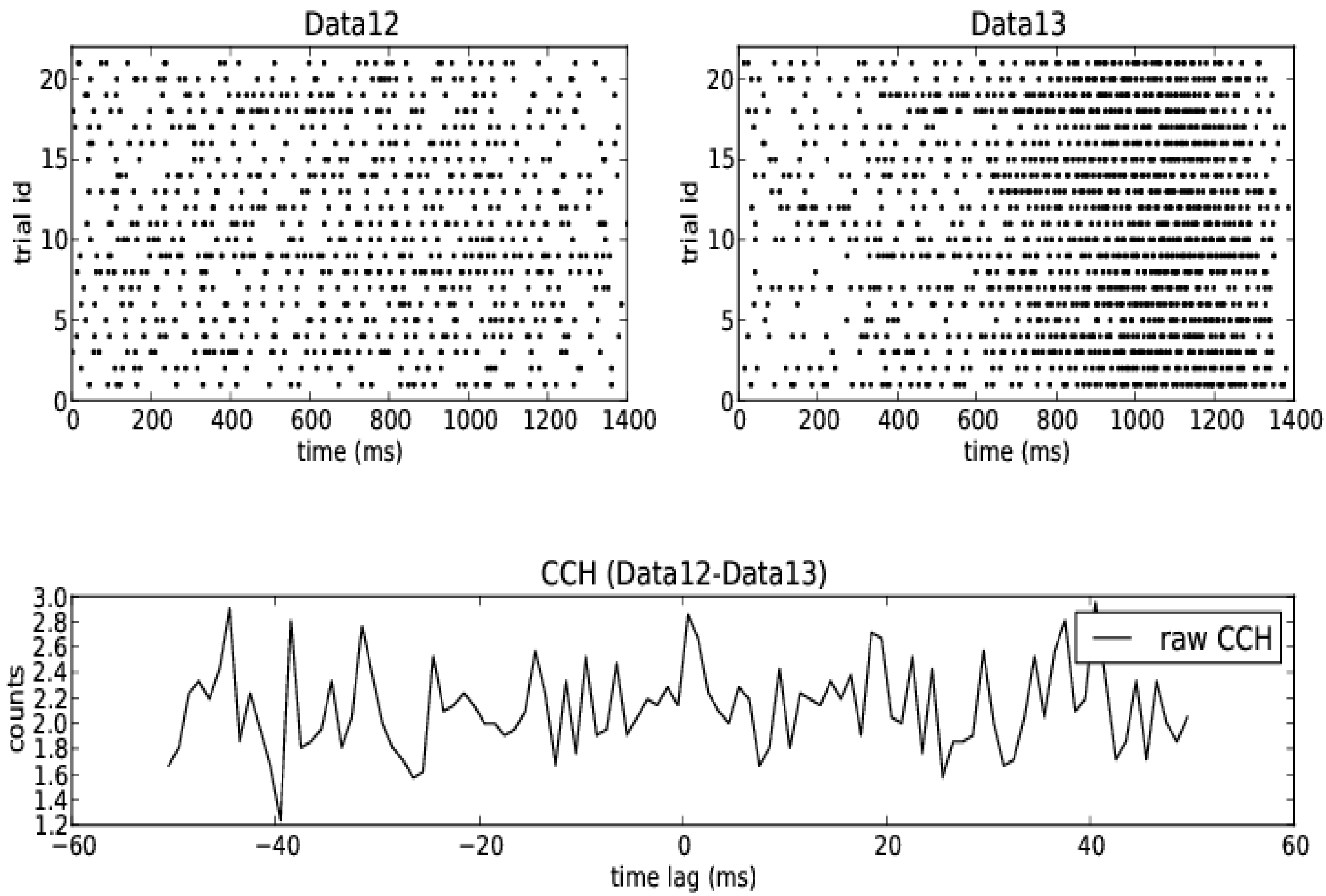
$$\rho_{12}(\tau) = \int s_1(t) \cdot s_2(t-\tau)dt$$

- In the case of spike trains, computation is performed directly on binned spike trains as **cross-correlation histogram (CCH)**



Cross-correlation histogram

Methods | CCH example



Methods | beyond chance?

- Trivially, the higher the rates, the more coincidences (just by chance!)
- Coherent changes in firing rates may induce a peak in a CCH
- How many chance coincidences are expected given the firing rates and their modulations?
  - Solution: compare to CCHs expected from uncorrelated data (‘**predictor**’)

Why and When Surrogates

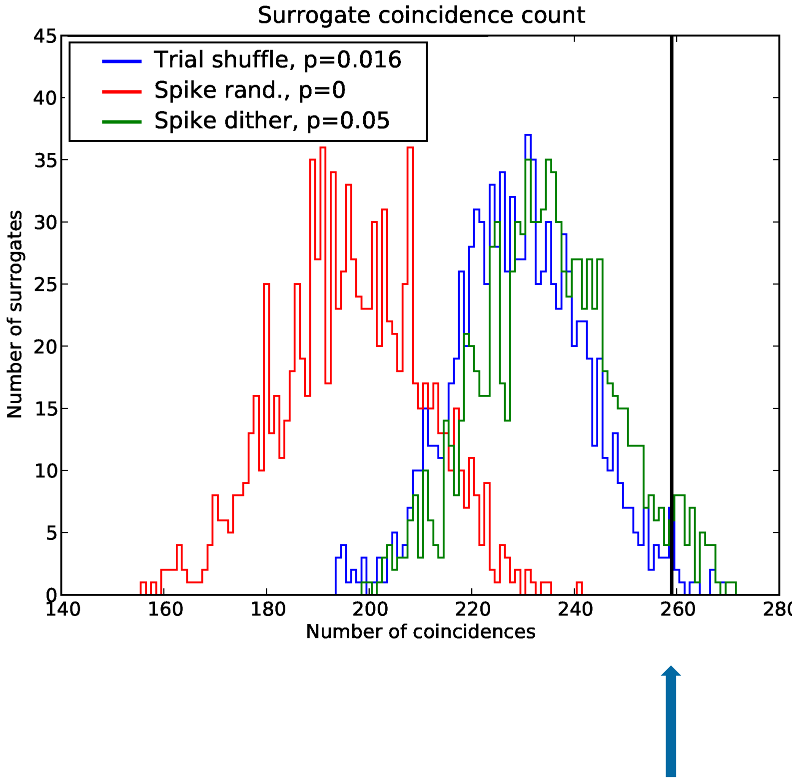
- Goal: test if *an empirical measure deviates from its predictor*
  - Requires knowledge of probability distribution of the predictor: **null distribution**
  - When unknown, **parametric** or **nonparametric** statistical methods may be used
    - Parametric tests: require model of the data and parameter estimates → often difficult to obtain

- Non-parametric surrogate statistical tests
  - Empirically estimate the null distribution by use of **surrogate data**, i.e., modified samples of the original data
    - Surrogate methods include bootstrap resampling, **randomization** approaches, and so on
  - In our case of correlation analysis: destroy potentially existing correlations but keep (ideally all) other statistical features intact

(In parts from: http://sccn.ucsd.edu/wiki/Chapter_5.2._Nonparametric_surrogate_statistics)

Practical procedure

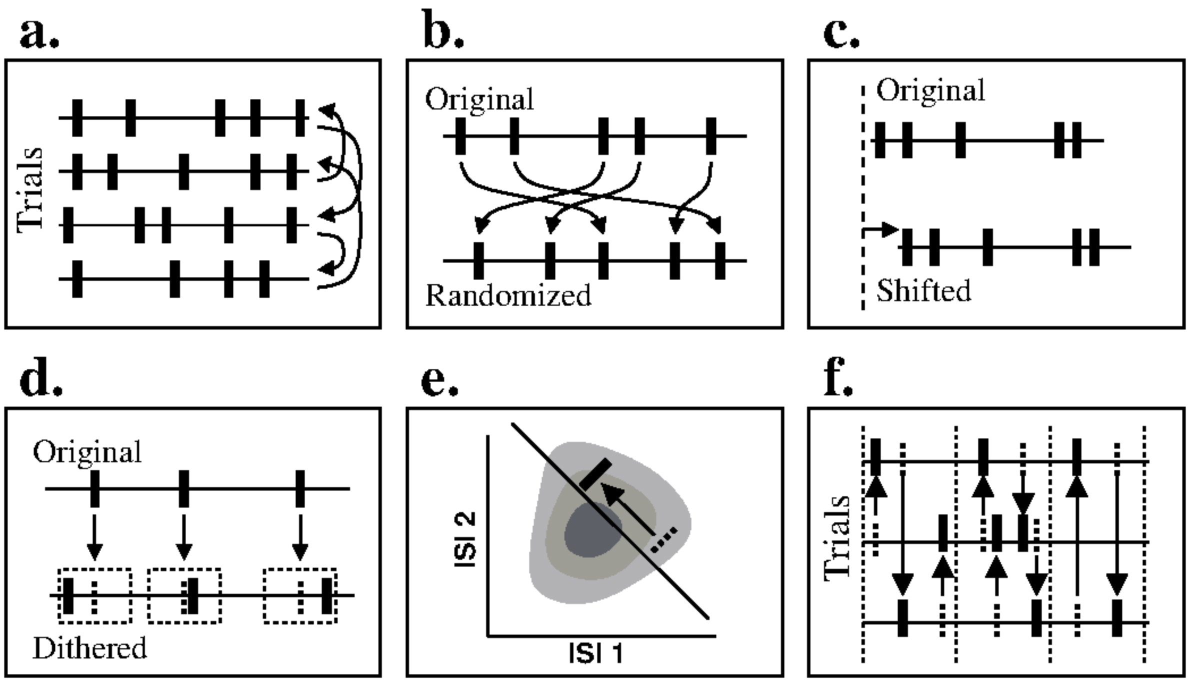
1. **Generate a surrogate** by manipulating the original data to destroy potential fine temporal correlation
2. **Compute the same measure** as from the original data
3. **Repeat steps 1 and 2** many times
4. **Derive the distribution** of the measure extracted from the surrogates
5. **Compare the empirical measure to the surrogate distribution**
6. **Derive significance** (p-value, surprise, etc.)



empirical count

Mitglied in der Helmholtz-Gemeinschaft

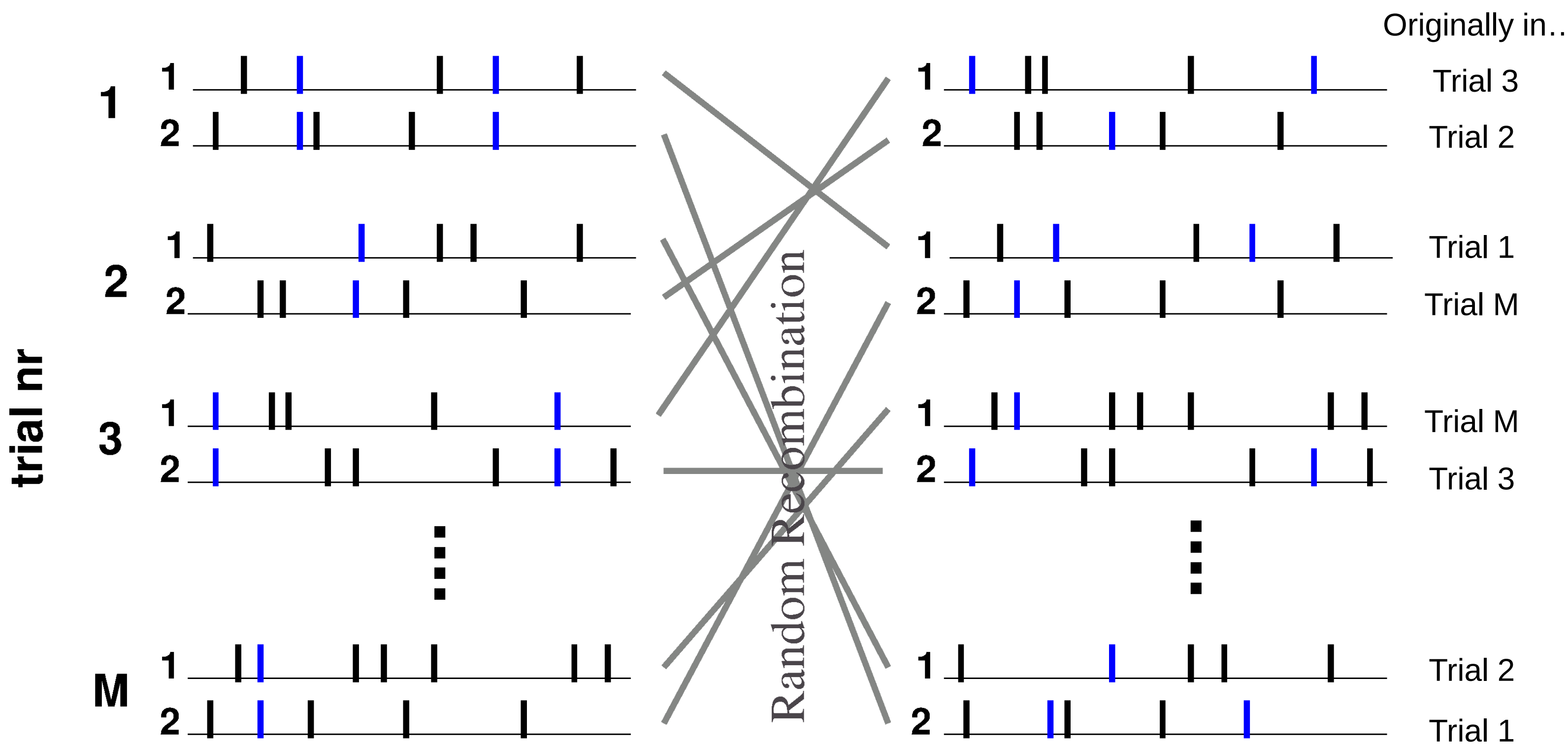
Surrogates for significance estimation



- More surrogates available / to be invented
- Concern: keep the changes in other statistical features of spike trains as little as possible

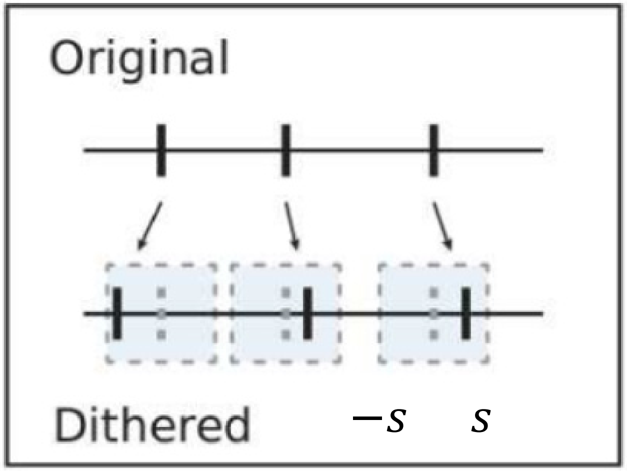
Grün (2009) *J Neurophysiol* (review)
Louis et al. (2010) *Front Comput Neuroscience*
Louis et al. (2010) in *Analysis of Parallel Spike Trains* (2010) Eds: Grün & Rotter, Springer

Trial shuffling



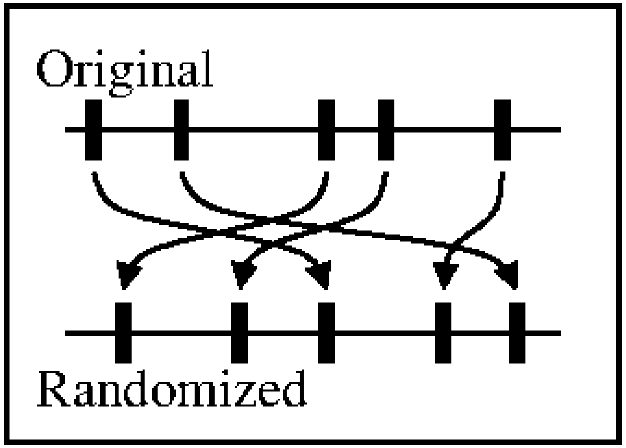
- Random recombination of trials
- **Effect**: spike trains are not changed, only their trial combination
- **Assumption**: stationarity across trials
  - For short-term stationarity: shift predictor = recombination with shifted trial IDs

Spike time dithering



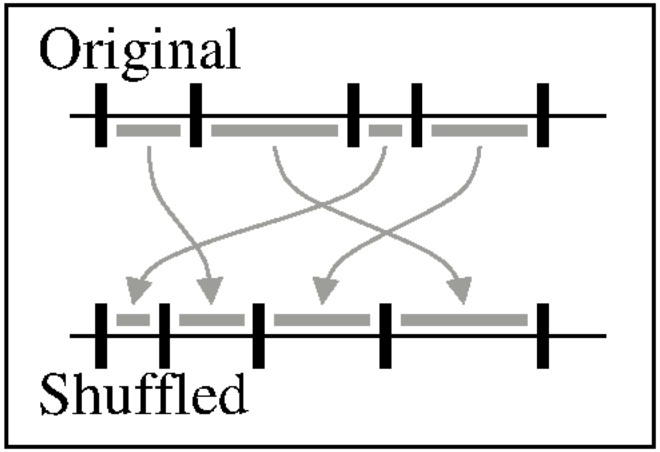
- Apply to each spike a small random shift with weighted probability within $[-s, s]$
  - Choice of s: larger than temporal jitter of correlation, small enough not to alter the firing rate modulations on a larger time scale
- **Effect**: ISIs modified, firing rate modulations smoothed
- **Assumptions**: stationarity on the time scale of the dither width

Spike time randomization



- Randomize times of spike occurrences
- **Effects**:
  - destroys ISIs (makes spike train become Poisson)
  - flattens the firing rate modulations
- **Assumption**: Poisson, stationarity

ISI randomization



- Randomize ISIs
- **Effects**:
  - keeps the distribution of ISIs
  - flattens the firing rate modulations
- **Assumption**: renewalty (more general than Poisson), stationarity

Pros-and-cons of different surrogate methods

TABLE 1. *Methods for implementing the null-hypothesis, divided into model based and data based*

		Method		Problems accounted for: Non-Stat Rate in Time	Problems accounted for: Cross-Trial Non-Stat	Problems accounted for: Non-Poisson	Assumptions	Conserves: Single Neuron	Conserves: Parallel Neurons	Destroys: Single Neuron	Destroys: Parallel Neurons	
Model based	A	Homogeneous Poisson process	Parameter estimation from trial average; Parameter estimation in single trials		(X)		• Poisson • stat	• average rate	• average rates of all neurons	• ISI • PSTH	• POPH	Spike timing across neurons
	B	Homogeneous model process			(X)	(X)	• Model process • stat	• average rate	• average rates of all neurons	• PSTH	• POPH	
	C	Inhomogenous Poisson process		(X)	(X)		• Poisson • Non-stat	• PSTH	• Co-var rate	• ISI	• POPH	
	D	Inhomogenous model process		(X)	(X)	(X)	• Model process • Non-stat	• PSTH • ISI	• Co-var rate		• POPH	
Data-based surrogates	E	Spike time randomization (within single trials)			X		• Poisson • stat	• SpC	• SpC co-var	• ISI • PSTH • Sp-tr struc	• POPH	
	F	ISI shuffling (within single trials)			X	X	• Renewal • stat rate • stat proc param	• SpC	• SpC co-var	• PSTH • Sp tr struc	• POPH	
	G	ISI shuffling (across trials)				X	• Renewal • stat rate • cr-tr stat	• tot SpC • tot ISI	• tot SpC per neuron	• PSTH • ISI • Sp-tr struc	• POPH	
	H	Trial shuffling		X			• cr-trl stat	• PSTH • ISI • Sp-tr struc	• tot POPH	• Trial ids	• POPH • SpC	
	I	Shift predictor		X	(X)		• Short-term cr-tr stat	• PSTH • sp tr struc • ISI	• tot POPH	• Trial ids	• POPH • SpC co-var	
	J	Spike shuffling across neurons (within trials)					• cr-tr stat • SpC co-var • Poisson			• PSTH • ISI • SpC • sp-tr struc		
	K	Spike exchange across neurons (within trials)					• stat rate • Poisson	• SpC	• POPH	• PSTH • ISI • sp-tr struc		
	L	Dithering		(X)	X	(X)		• sp-tr struc (approx) • SpC • ISI (smoothed) • PSTH (smoothed)	• POPH (smoothed)			
	M	Soft dithering (according to ISI distribution)		(X)	X	X		• sp-tr struc (approx) • SpC • ISI • PSTH (smoothed)	• POPH (smoothed)			
	N	Shifting spike trains of neurons against each other		(X)	X	X		• Sp-tr struc • SpC (approx) • PSTH (smoothed)	• POPH (smoothed)			

Grün (2009) *J Neurophysiol*

Pros-and-cons of different surrogate methods

- Example drawback: applying **spike time dithering** on data to be discretized can lead to spike count reduction

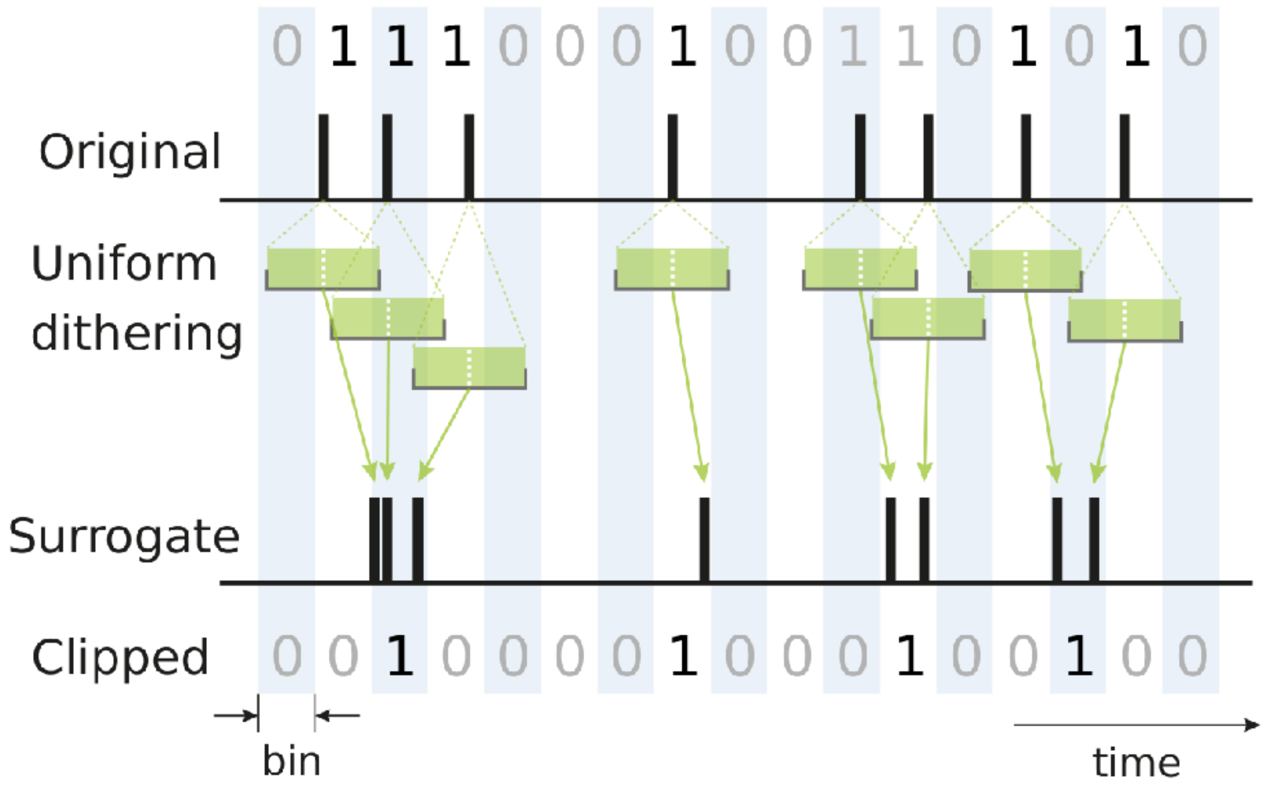
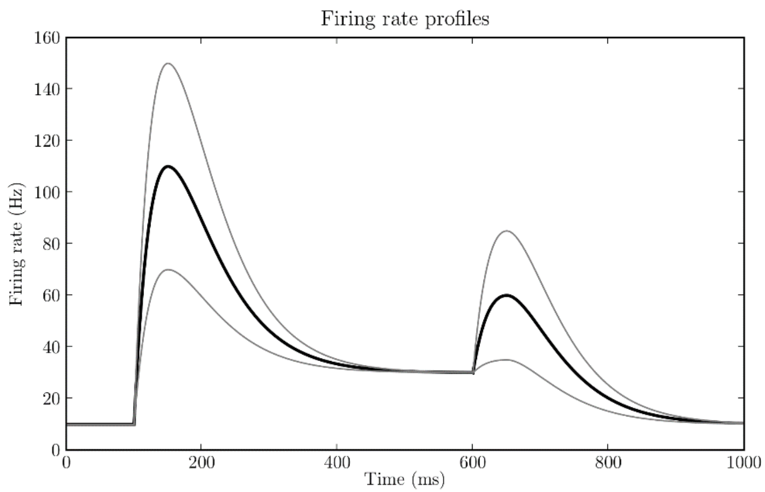


Figure by Sebastian Lehmann, in Stella et al. (2022)

Surrogate performance | test data



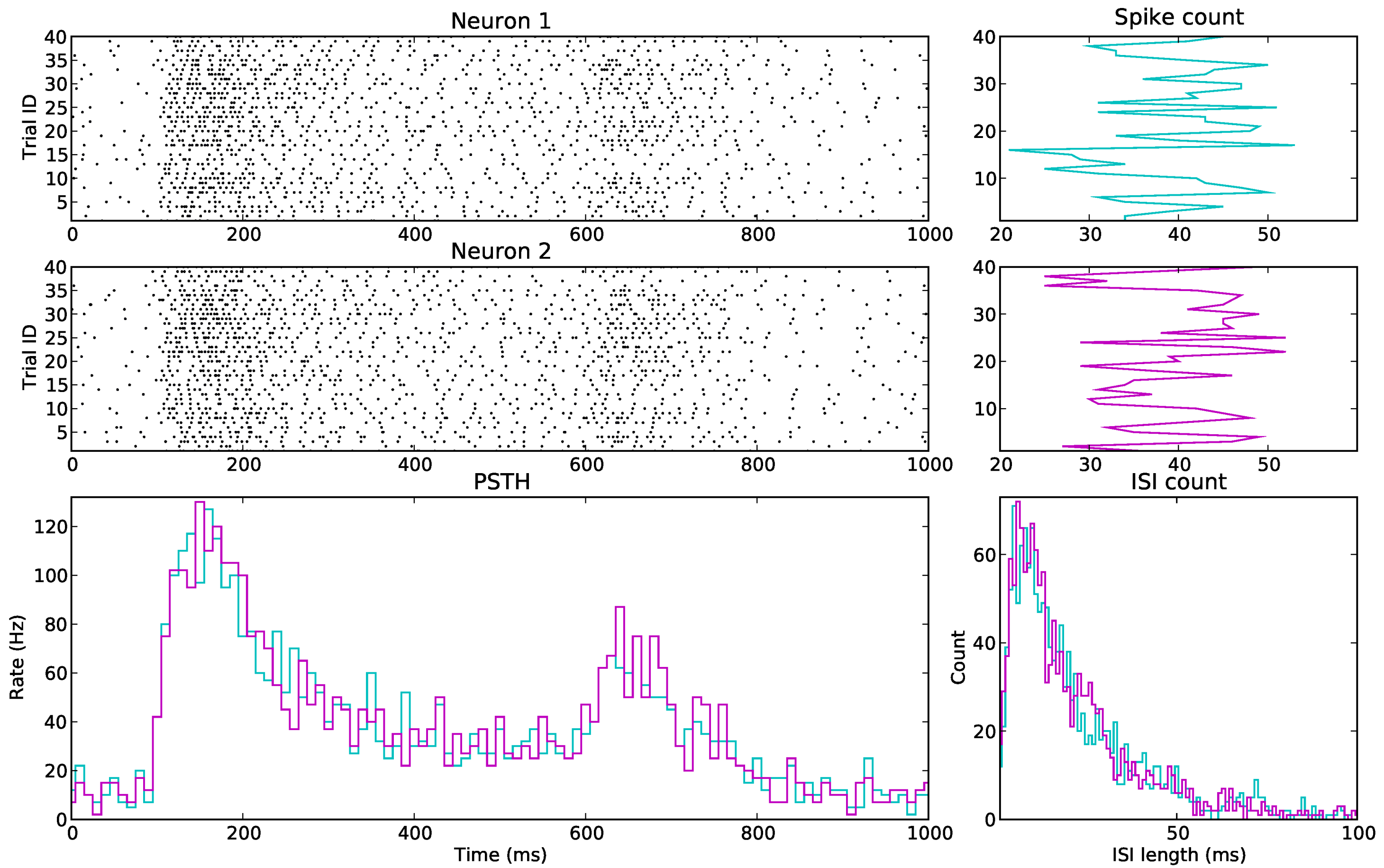
Type	Process	Nonstat. in time	Cross-trial nonstat.	γ	Δ
1	Poisson	no	no	1	0
2	Poisson	yes	no	1	0
3	Poisson	no	yes	1	0.235
4	Poisson	yes	yes	1	0.5
5	Gamma	yes	yes	3	0.5

Louis et al. in *Analysis of Parallel Spike Trains* (2010)
Eds: Grün & Rotter, Springer

- To evaluate the performance of different surrogate methods, a test data set is generated
  - Non-stationary firing rates according to a profile
  - Cross-trial variations by random selections (per trial) of rate modulation depth Δ
  - Different regularities of the ISIs by gamma processes of different shape factors γ
- Correlations are introduced by inserting coincident spikes in a pair of spike trains at a given rate

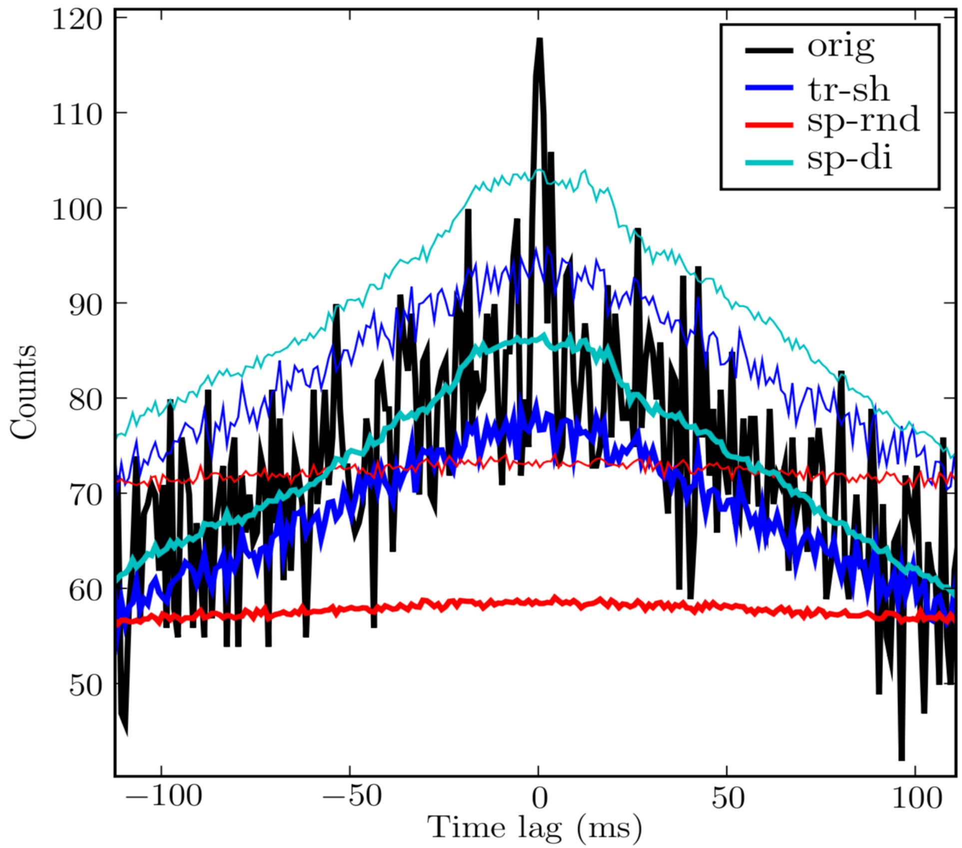
Surrogate performance | test data

An example of type 5 data



Louis et al. in *Analysis of Parallel Spike Trains* (2010) Eds: Grün & Rotter, Springer

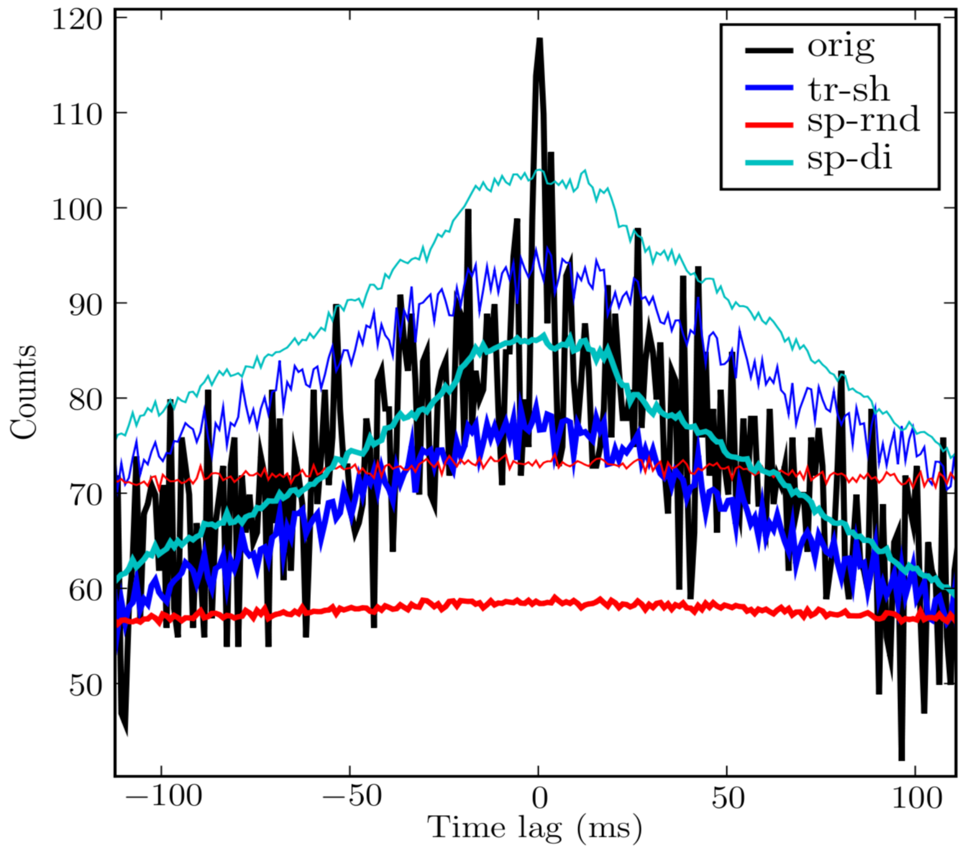
Surrogate performance | CCH



Louis et al. in *Analysis of Parallel Spike Trains* (2010)
Eds: Grün & Rotter, Springer

- Two temporally different components in the original data
  - Broad peak: due to the non-stationarity of the firing rate
  - Narrow peak at zero-lag: fine temporal correlation

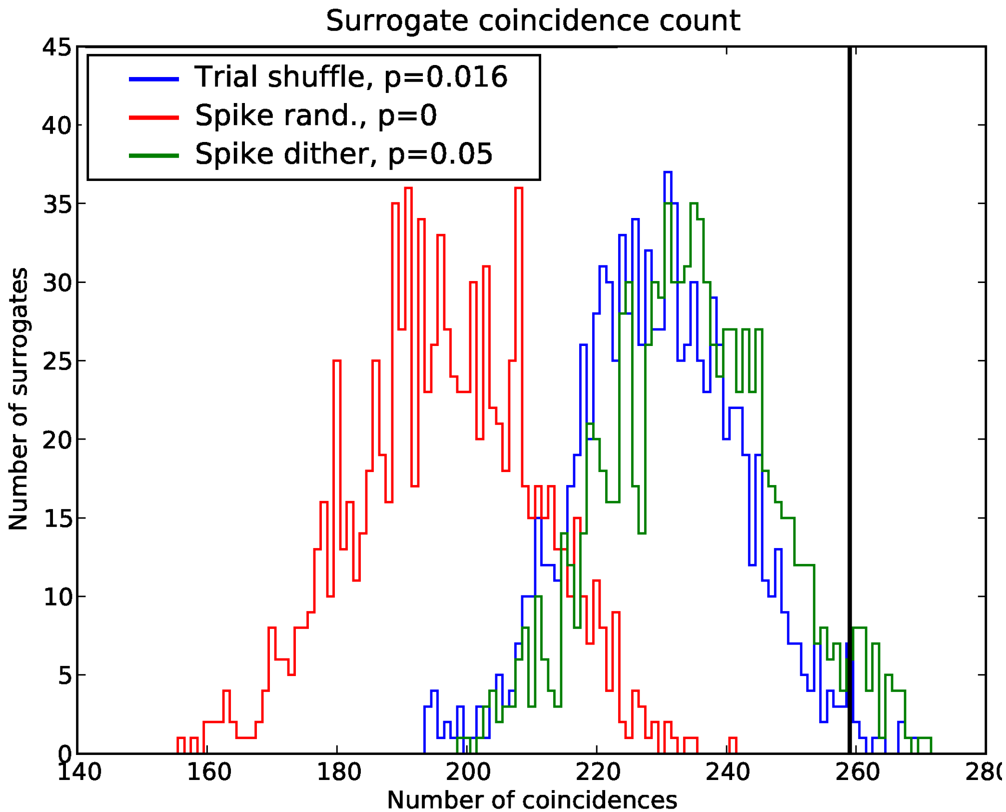
Surrogate performance | CCH



Louis et al. in *Analysis of Parallel Spike Trains* (2010)
Eds: Grün & Rotter, Springer

- Spike time randomization
  - Flat CCH – due to destruction of firing rate changes
- Trial shuffling
  - Under-estimation of the amplitude of the rate peak due to the variability across trials
- Spike time dithering
  - Reproduces the broad peak

Surrogate performance | zero-lag synchrony



Louis et al. in *Analysis of Parallel Spike Trains* (2010)
Eds: Grün & Rotter, Springer

- Empirical coincidence count at 258
  - Its percentile score in each surrogate distribution is shown in the legend
- With a 5% significance threshold, the empirical count is significantly large in comparison to all types of surrogates
- **But mostly due to wrong reasons** – all but spike time dithering tend to lead to false positives!

Methods | summary

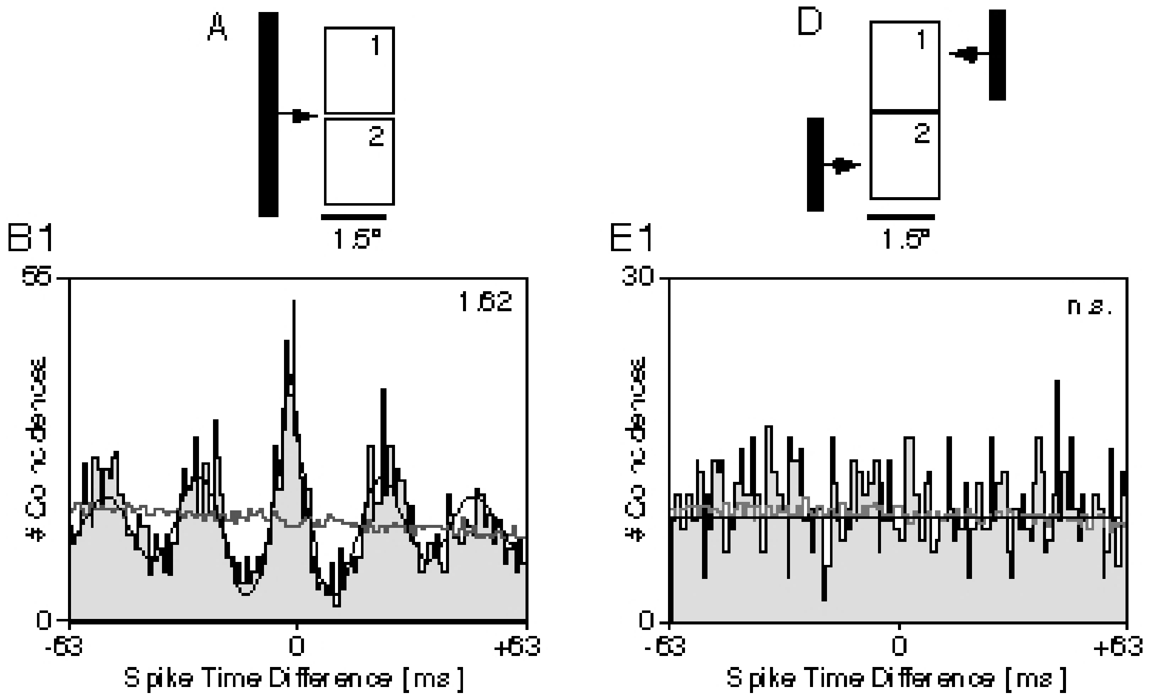
- **Cross-correlation histogram** (CCH) is a standard tool for examining synchronized or delayed spike correlation.

- Comparison to **surrogate data** allows to differentiate excess correlation from chance correlation, which occurs just by chance.
  - Choosing an appropriate surrogate method is crucial for drawing proper conclusions

Outline

- Methods
  - Cross-correlation analysis
  - Significance test
- **Applications**
  - Relation to gestalt perception
    - Cat V1 data (response to visual edges)
    - Monkey MT data (response to visual movement)
  - Relation to network architecture
    - Rat somatosensory cortex (anesthesia)
    - Human neocortex (during sleep)

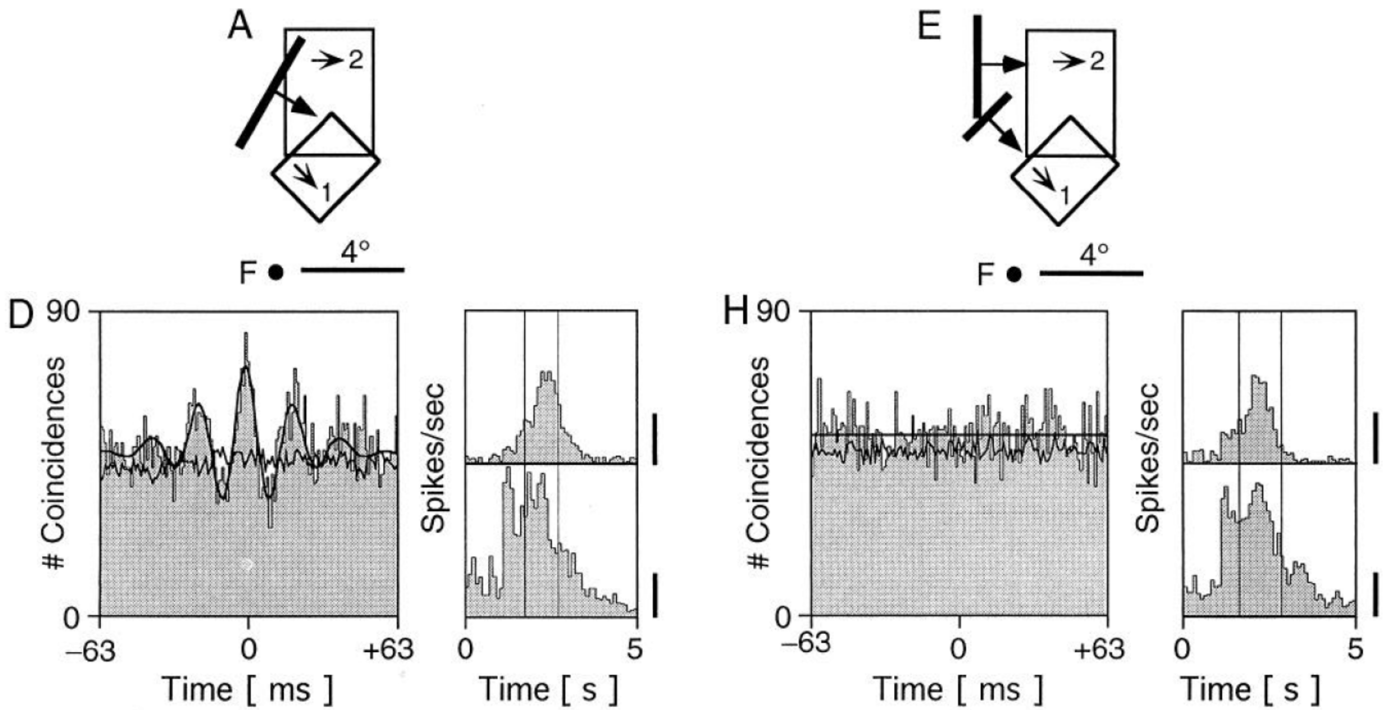
Application | relation to gestalt perception



Freiwald et al. (1995) NeuroReport 6: 2348--2352

- Simultaneous recording from pairs of single units in the primary visual cortex (A17) of cats
- Long bar condition: **synchronized spike response**
- Dual bar condition: absence of synchronization

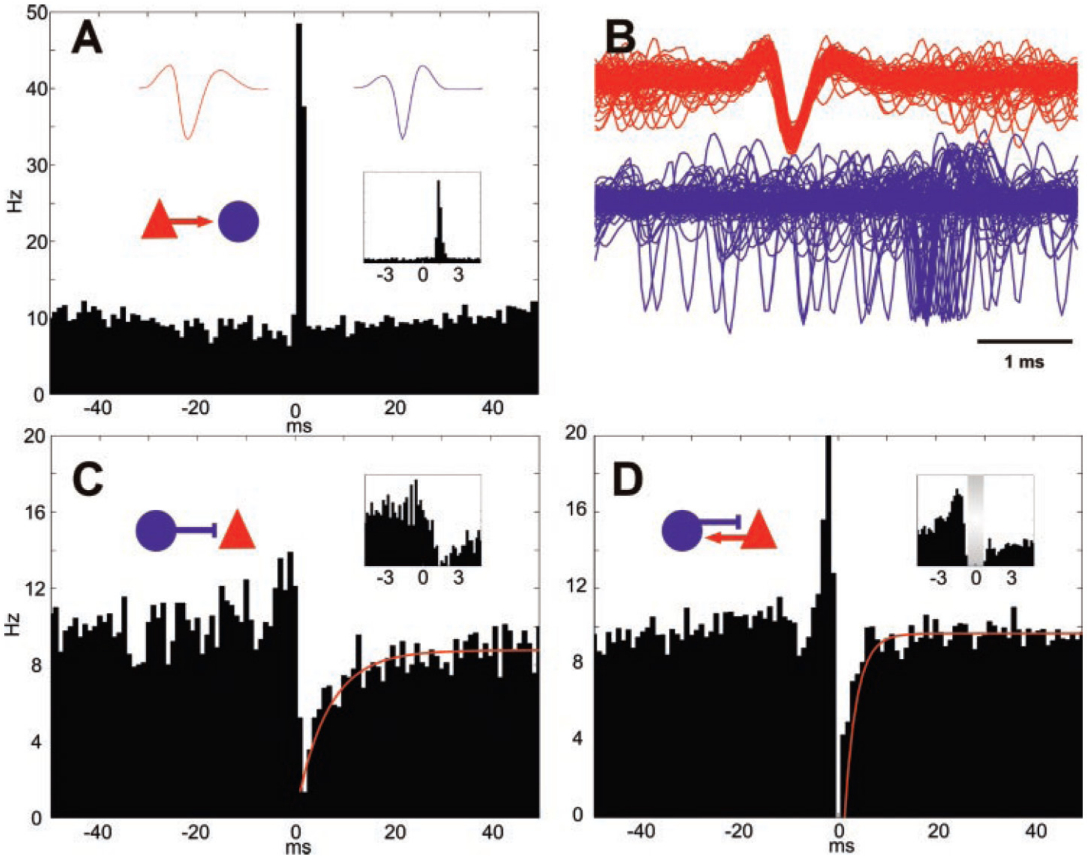
Application | relation to gestalt perception



Kraiter and Singer (1996) J Neurosci 16:2381-2396

- Simultaneous recording from pairs of single units in area MT of monkeys
- Long bar condition: **synchronized spike response**
- Dual bar condition: absence of synchronization

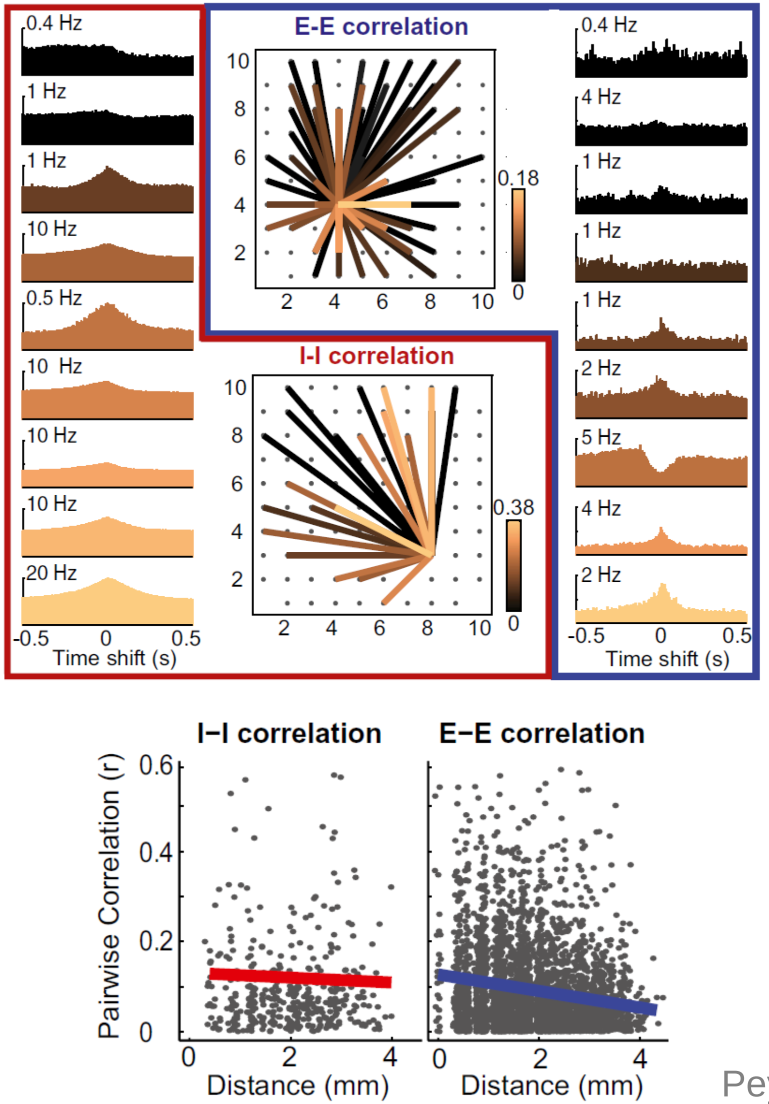
Application | relation to network architecture



Bartho et al. (2004) J Neurophysiol 92:600-608

- Simultaneous recording from multiple single units in rat somatosensory cortex using a 64-ch electrode array
- ~0.25% of the recorded cell pairs showed short-latency peak and/or trough in their CCHs
- **Short-latency peak → excitatory connection**
- **Short-latency trough → inhibitory connection**

Application | relation to network architecture



- Simultaneous recording from multiple single units in the middle temporal gyrus of epilepsy patients using a 10x10 grid of electrodes

- Correlation between inhibitory neurons → **constant over distance**

- Correlation between excitatory neurons → **decay with distance**

Peyrache et al. (2012) PNAS 109:1731-1736

JÜLICH FORSCHUNGSZENTRUM

Summary

- **Cross-correlation histogram** (CCH) is a standard tool for examining synchronized or delayed spike correlation.
- Comparison to **surrogate data** allows to differentiate excess correlation from chance correlation, which occurs just by chance.
- Conversing evidence suggests that gestalt perception requires binding of single unit activities via spike synchrony.
- The type and direction of synaptic connections between neurons can be inferred from the shape of CCH.