# Multivariate information-theoretic measures reveal directed information structure and task relevant changes in fMRI connectivity

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**Presented at Charles Sturt University**

18/10/2012

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# Publication

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"Multivariate information-theoretic measures reveal directed information structure and task relevant changes in fMRI connectivity"

*Journal of Computational Neuroscience* (Special issue on "Methods of Information Theory in Neuroscience Research"),

vol. 30, pp. 85-107, 2011;

http://dx.doi.org/10.1007/s10827-010-0271-2 - http://bit.ly/ho2ofr

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# Interregional directed information structure: overview

- Computational neuroscience
  - Computational analysis of brain imaging data
  - Neuroscientist: "How can we analyse data to understand how brain regions interact? What does this tell us about, e.g. disease?"
  - Computer scientist: "How can we describe computation in the brain? What does this tell us about computation in nature?"
- Task: establish directed interregional information structure from time-series brain imaging data
  - Also known as effective networks
  - Taking into account some particular requirements: interregional level, capturing multivariate interactions, non-linearity, small amount of data …
- Method: directed information transfer
  - Plus enhancements including multivariate analysis and statistical significance measurements
- Application: a visuomotor tracking task
  - Directed interregional structure, with movement planning regions driving visual and motor control

# Directed information structure task

- Take a multivariate time series measured across different brain regions during a cognitive task. Each region contains many measured variables (in fMRI these are voxels)
- Infer the directed information structure between the regions that supports this task.

There is much previous work on establishing effective networks, but none meets *all* of the following **challenges/requirements**:

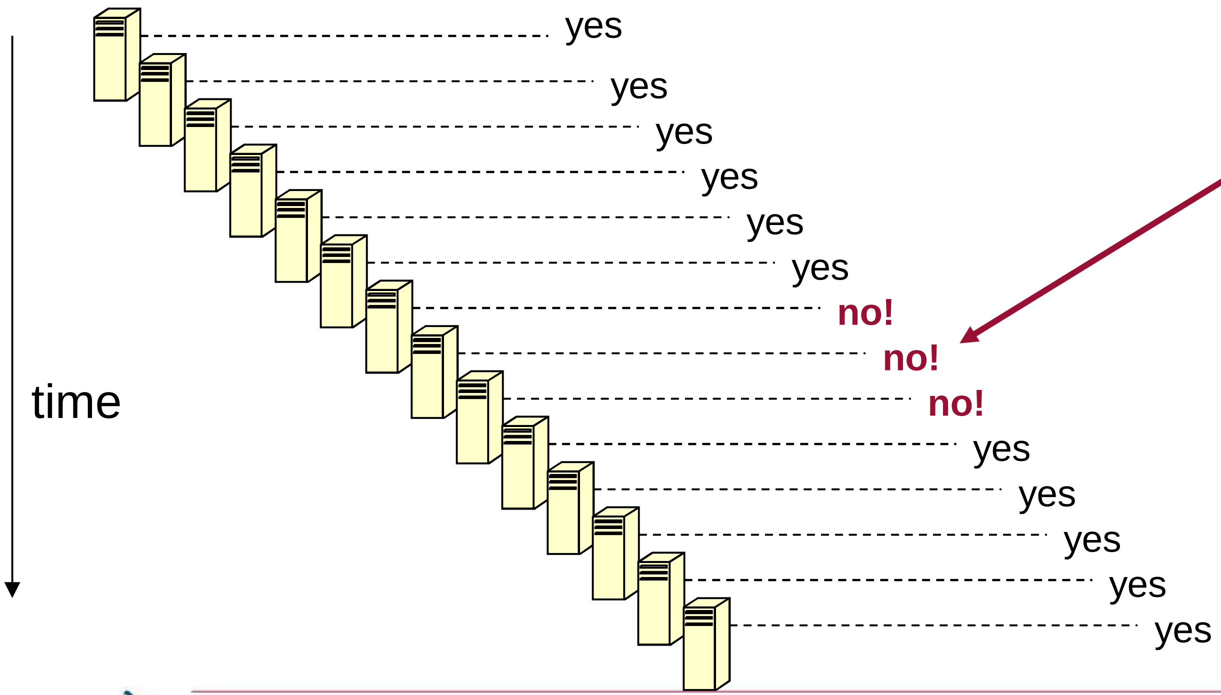
- Explicitly examines information transfer
- Capture directionality
- Capture non-linear interactions
- Capture collective interactions
- Infer at the regional level
- Handle small amounts of data
- Distinguish a weak relationship from none
- Don't assume an underlying model

Our approach has **properties to meet these** challenges/requirements:

- Uses transfer entropy
- Asymmetric analysis
- Information-theoretic (i.e. non-linear)
- Multivariate
- Infers at the regional level
- Uses dynamic kernel width (Kraskov)
- Uses statistical significance
- Information-theoretic (i.e. model-free)

# Information theory: the natural domain

- (Shannon) Entropy is a measure of uncertainty
- Intuitively: if we want to know the state of a variable, there is uncertainty in what that state is (measured in bits)
  - e.g. Is the web server cam.ac.uk running?



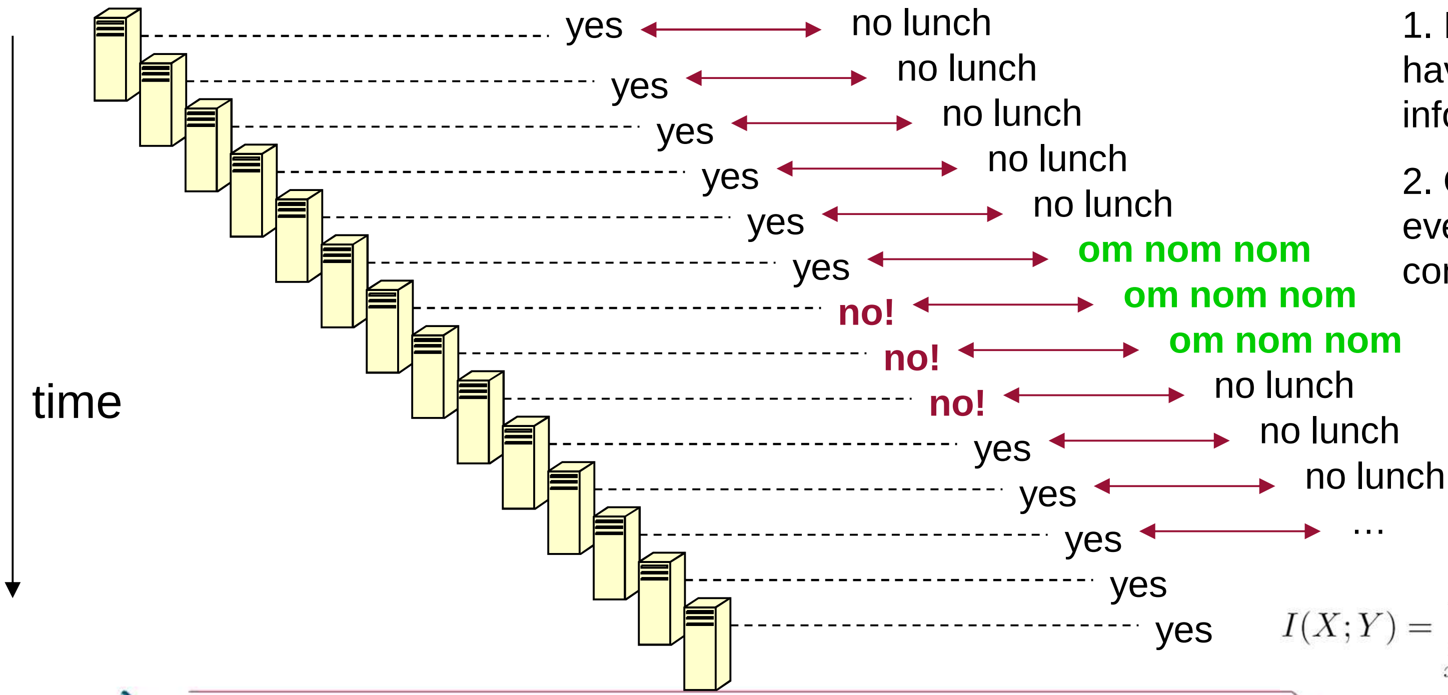

1. There is more uncertainty in more rare events

2. There is more average uncertainty when there is a balance in event probabilities

$$H(X) = -\sum_{x \in \mathcal{X}} P(x) \log P(x)$$

# Information theory: the natural domain

- Information is a measure of uncertainty reduction
- Intuitively: common information is the amount that knowing the value of one variable tells us about another
  - e.g. How much common info b/w if IT guy is at lunch and the web server running?



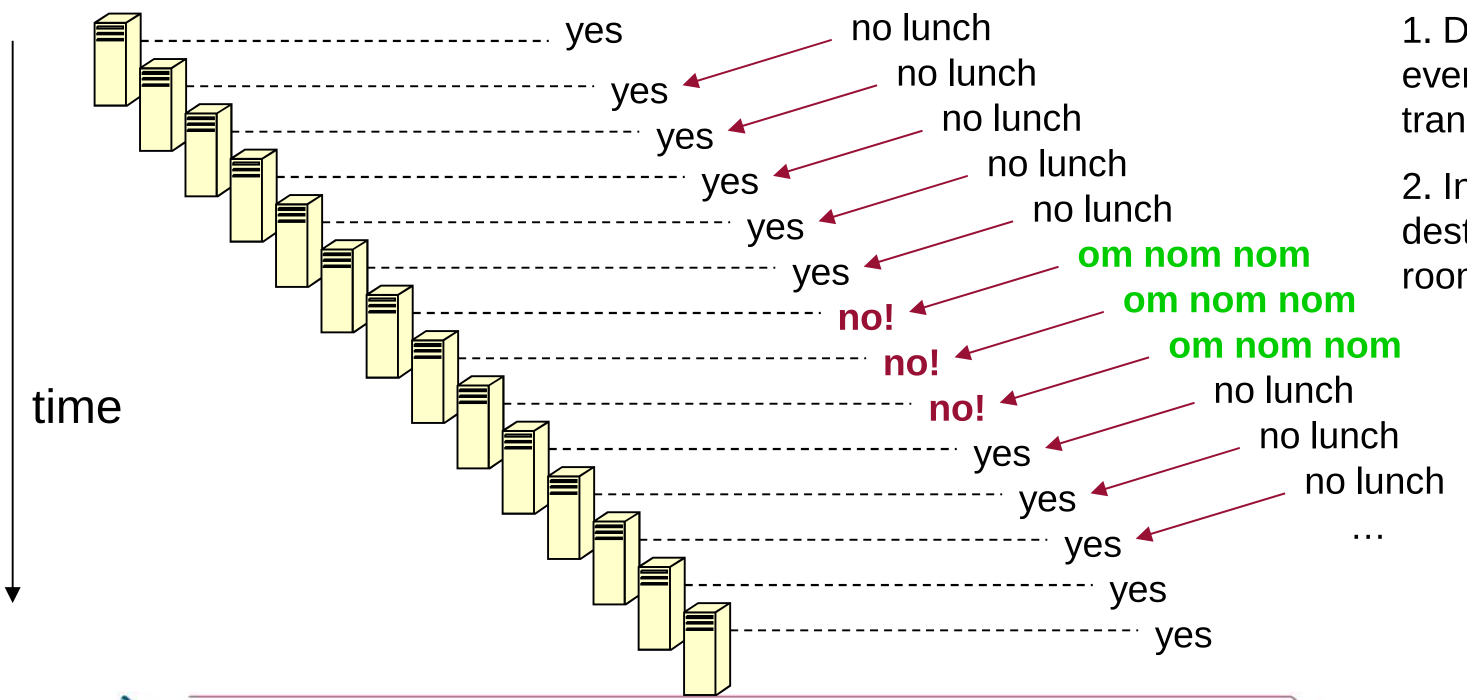

1. Independent events have no common information

2. Completely dependent events have max common info

$$I(X;Y) = \sum_{x \in \mathcal{X}} \sum_{y \in \mathcal{Y}} P(x,y) \log \frac{P(x,y)}{P(x)P(y)}$$

# Information theory: the natural domain

- Information transfer measures directed coupling between time series
- Intuitively: the amount of information that a source variable tells us about a destination, that was not already contained in the destination.
  - e.g. How much does knowing IT guy is at lunch tell us about web server running, that we didn't already know from its previous state?

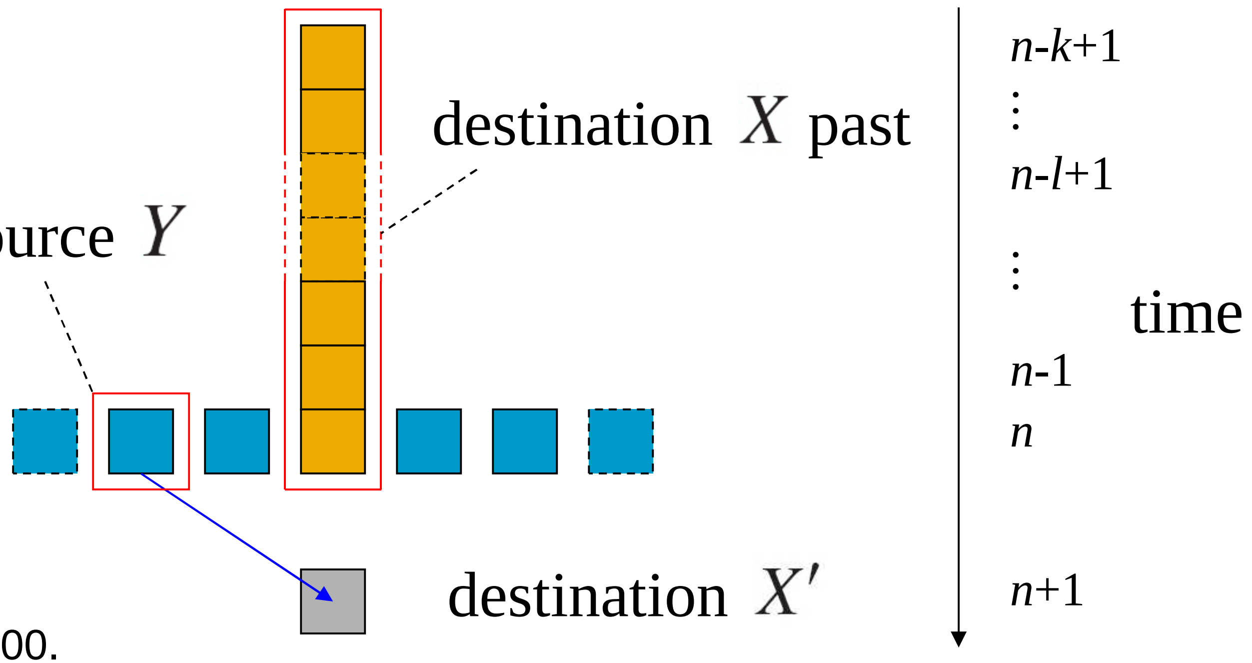



1. Directionaly dependent events have max info transfer

2. Internal predictabiity in destination allows no room for transfer

# Information transfer

$$T_{Y \to X'} = I(Y;X' | X) = H(X' | X) - H(X' | X,Y)$$

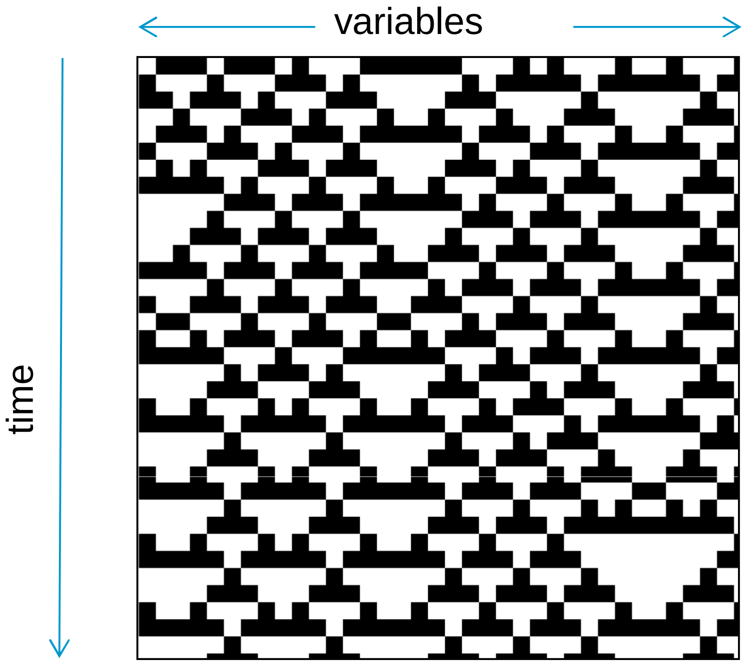



**Transfer entropy**

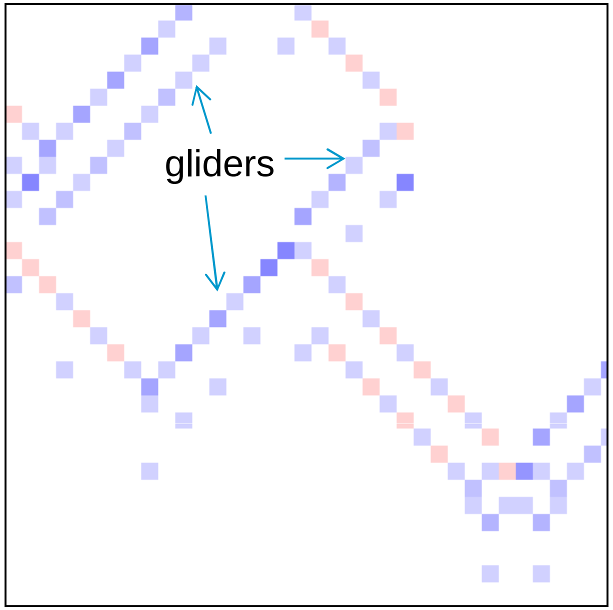
Schreiber, PRL 2000.

Explicitly info transfer, non-linear, directional, model-free

# Information transfer in cellular automata



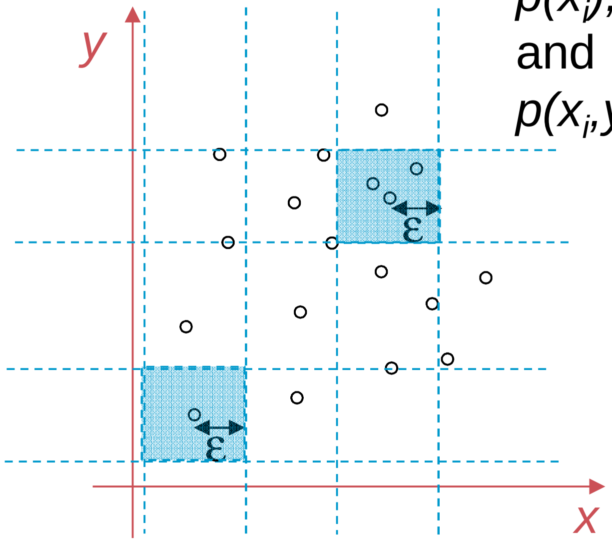

ECA rule 54



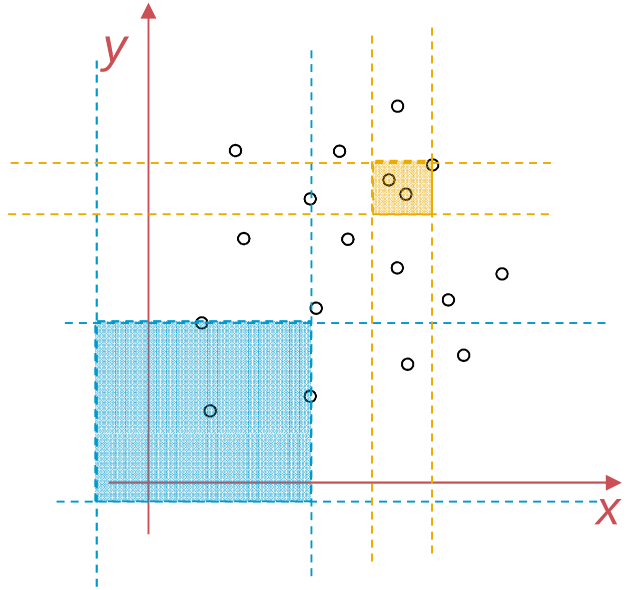

Local transfer to left

- Transfer entropy aligns with our qualitative understanding of information transfer (Lizier et al, PRE 2008)
  - i.e. gliders are dominant information transfer entities.

# Information measures on continuous-valued variables




$p(x_i)$, $p(y_i)$
and
$p(x_i,y_i)$ ?

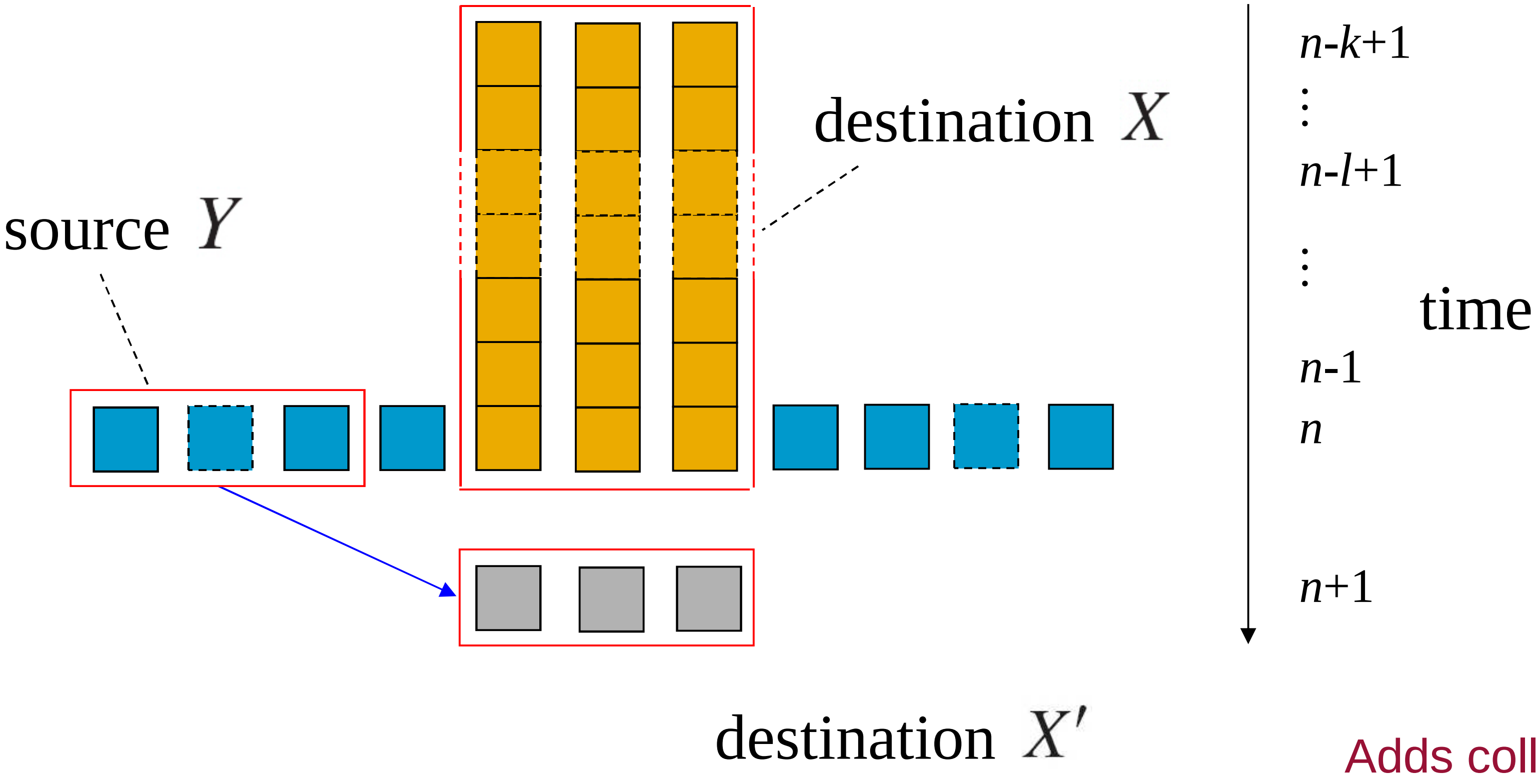



- Kernel estimation
  - Fixed box width
  - "How does knowing *x* within ε help me predict *y* within ε?"
- Kraskov technique (PRE, 2004)
  - Dynamic box width and bias correction
  - "How does knowing *x* within its *k* closest samples help me predict *y* within its *k* closest samples?"

Useful for small data sets

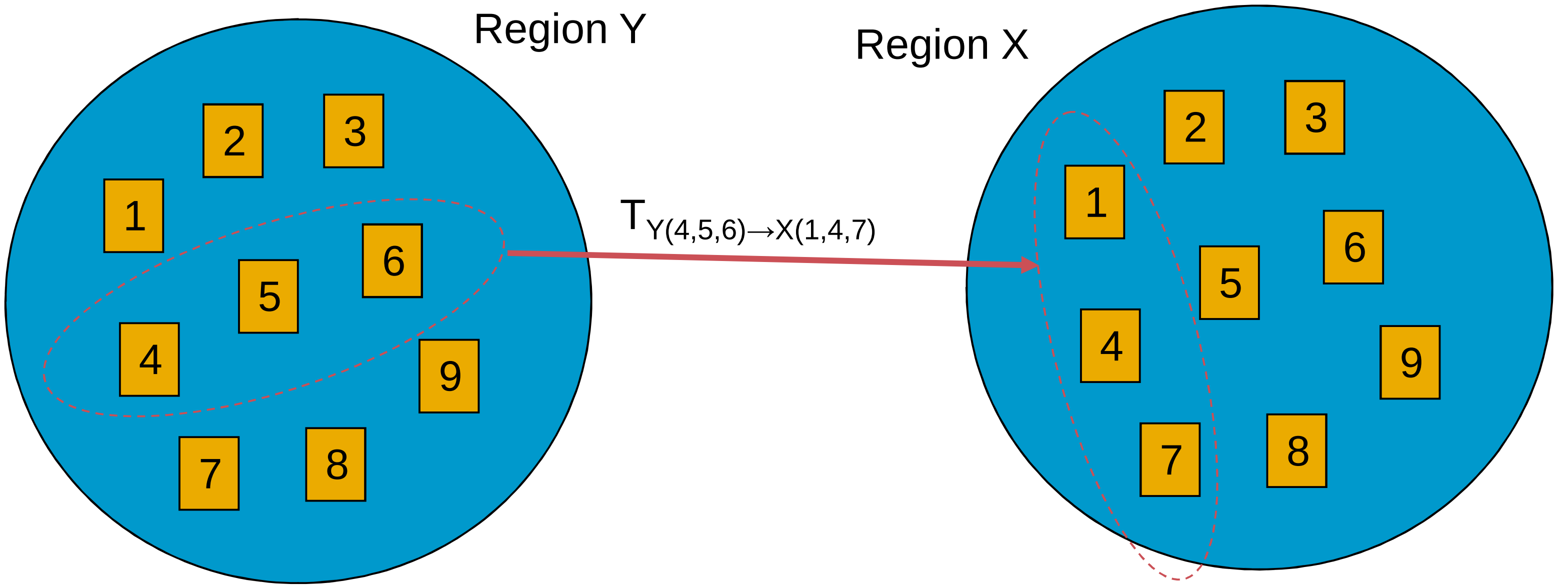
# Multivariate information transfer

$$T_{Y \to X'} = I(Y; X' | X) = H(X' | X) - H(X' | X, Y)$$




Adds collective interactions

# Interregional multivariate information transfer



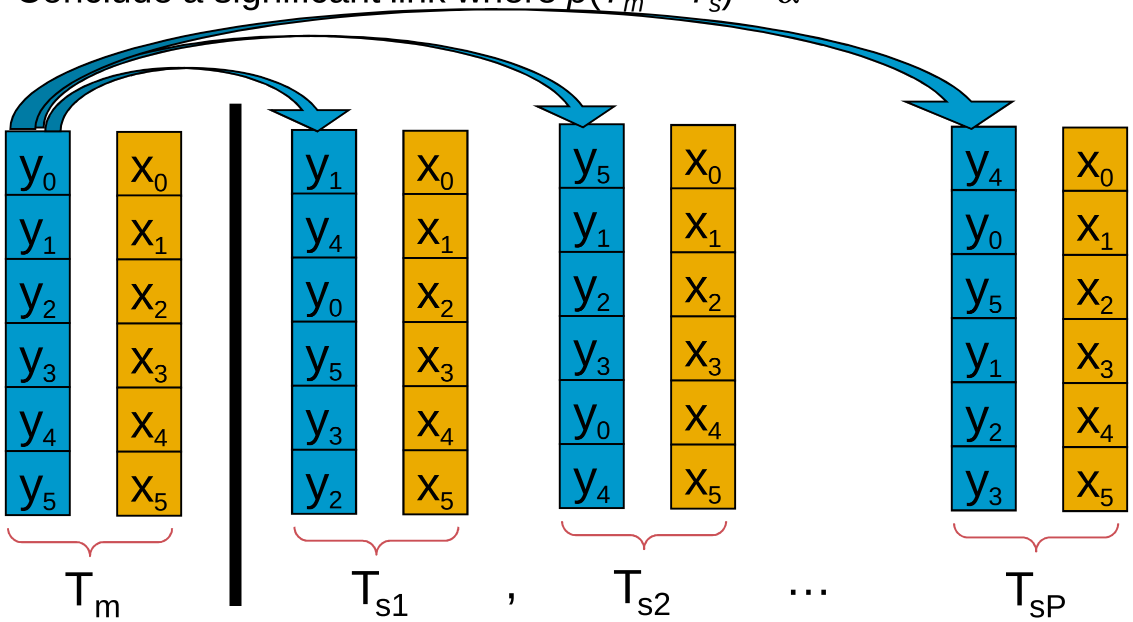

Interregional Transfer is the average Transfer Entropy from each pair *i* of *v* voxels in region *Y* to each pair *j* of *v* voxels in region *X*.

$$T_{k,v}(\mathbf{Y} \rightarrow \mathbf{X}) = \langle T_k(\mathbf{Y}_i \rightarrow \mathbf{X}_j) \rangle_{i,j}$$

Adds interregional level

# A method of inferring interregional links for the directed information structure

1. Inferring a directional link with transfer entropy (Chávez et al, 2003)
   - Compute the significance of the measured transfer entropy $T_m$ by comparing to a population of surrogate values with relationship between source and destination destroyed.
     Null hypothesis: no temporal relationship b/w source and destination.
   - Compute $P$ surrogate TE values $T_s$ by permuting the source observations $y_n$ with respect to the destination state transitions $x^k_n \rightarrow x_{n+1}$.
   - Conclude a significant link where $p(T_m < T_s) < \alpha$




From: Chávez et al, 2003, Verdes 2005, Vicente 2011, etc

# A method of inferring interregional links for the directed information structure

2. Extend inference to multivariate transfer entropy (trivial)
3. Extend inference to interregional transfer
   - To generate each sample TE value:
     1. Permute **all** of the source variables together against the destination region.
     2. Compute $T_{Yi \rightarrow Xj}$ for each required set (*i*,*j*) with the same permutation of source variables.
   - The method is applicable using either MI or TE as a basis
4. Extend inference to group level:
   - Use the binomial distribution to infer whether the number of individuals who had a significant link for that region pair was a significant number (with the null hypothesis that individual links may be inferred by chance alone).

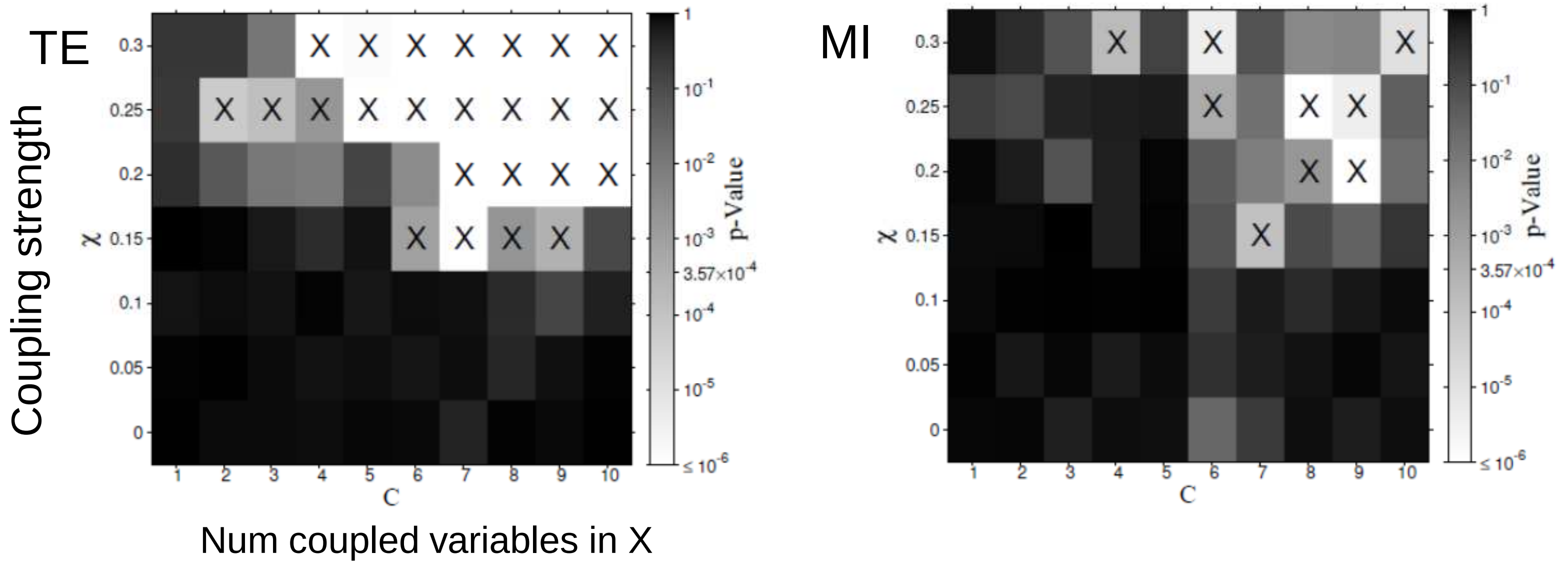
- We can analyse modulation of the structure with respect to an experimental variable (by assessing significance of the correlation against surrogate correlations from permuted data sets)

Distinguishes the existence of a relationship from no relationship; adds robustness to small data sets

# Verification of the technique

- Performed using coupled Gaussians:
  - **Y** determines *C* variables in **X** via non-linear pairwise coupling; noise added

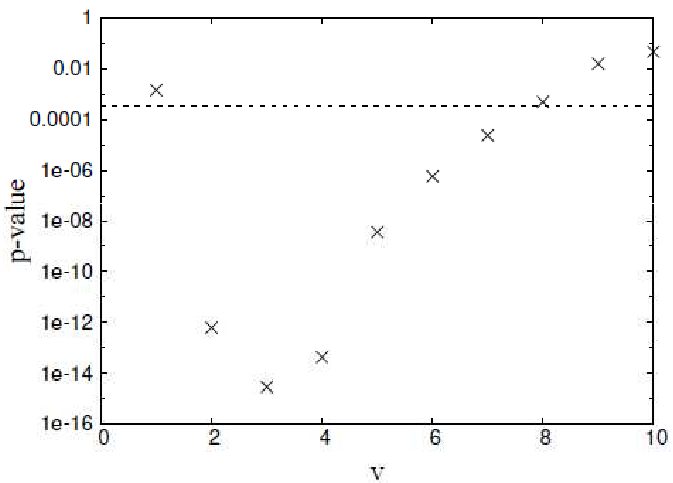
$$x_{i,n+1} = \begin{cases} \epsilon_x x_{i,n} + \chi y_{j,n} y_{l,n} + (1-\epsilon_x-\chi) g & \text{for } i \leq C \\ \epsilon_x x_{i,n} + (1-\epsilon_x) g & \text{for } i > C \end{cases}$$




- TE detects relationship more consistently, at weaker couplings
- No false positives in reverse direction.

# Verification of the technique (continued)

- Demonstrated that the limitations of the technique when there is insufficient data:
  - Importantly, the technique is robust to this because it simply makes no inferences when there is not enough data



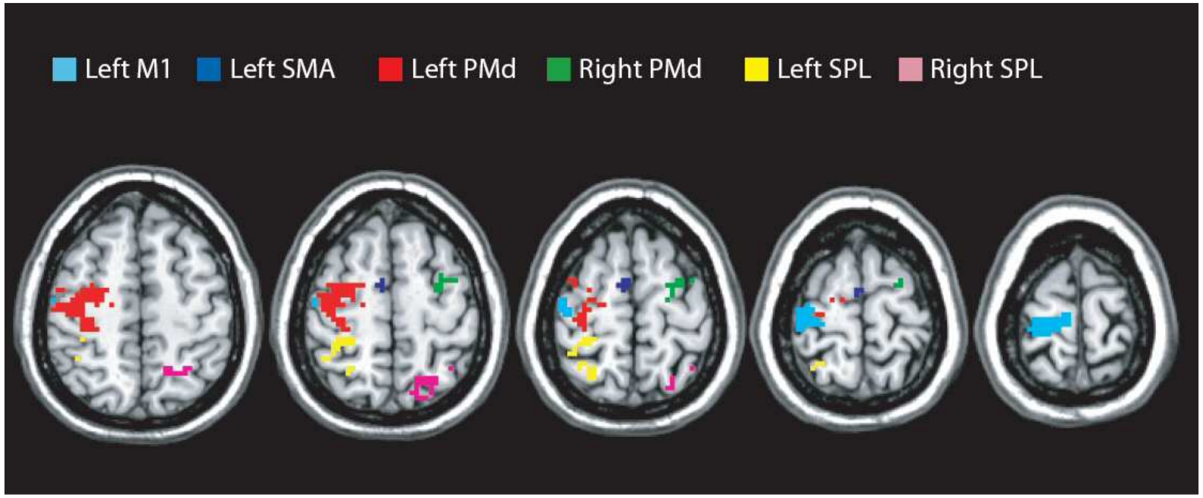

Demonstrated effectiveness of multivariate analysis

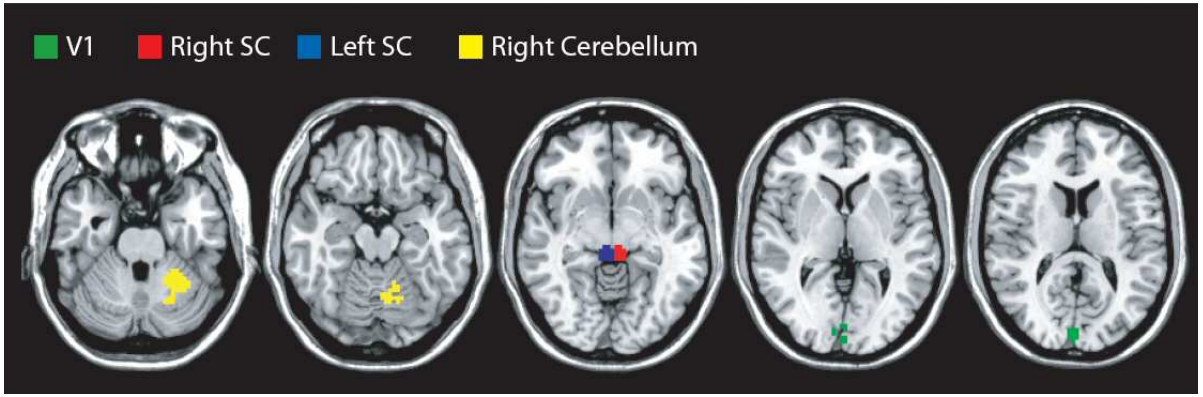
- Demonstrated some robustness to undersampling
- Demonstrated some weakness to false positive situations (pathway structure and common cause) though identified the conditions under which this occurred and suggested techniques to mitigate the effect (future work).

# Application to an fMRI data set

- Cognitive task: visuomotor tracking
  - control a mouse with right hand to track a moving target on a computer screen
  - 4 levels of difficulty; changed after 16.8 second blocks.
  - 8 subjects
  - functional Magnetic Resonance Imaging (fMRI) measurements
  - resolution: 3mm, typically hundreds of voxels in each regions.
  - 1 image every 2.8 seconds.
  - 20 blocks of 7 images gives 140 images per difficulty level.
  - data pre-processed (standard motion correction and spatial normalization) and 11 localized regions of interest selected using a general linear model (GLM) and general interest for tracking (F-test) analysis.

# fMRI-BOLD imaging




M1 – primary motor cortex

SMA – Supplementary motor area

PMd – pre-motor dorsal

SPL – superior parietal lobule

V1 – primary visual cortex

SC – superior colliculus

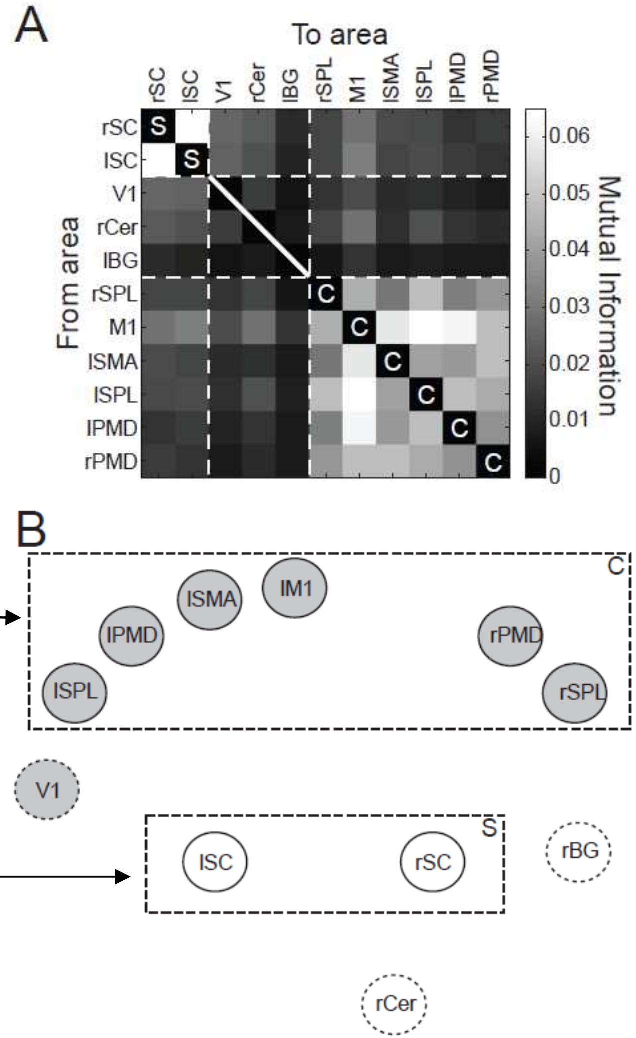
These regions encompass: Movement planning, visual perception and control, and execution

# Undirected structure (inferred by MI technique)

- All region pairs had a significant undirected relationship at the group level during the task; but clusters could be identified by spectral reordering.

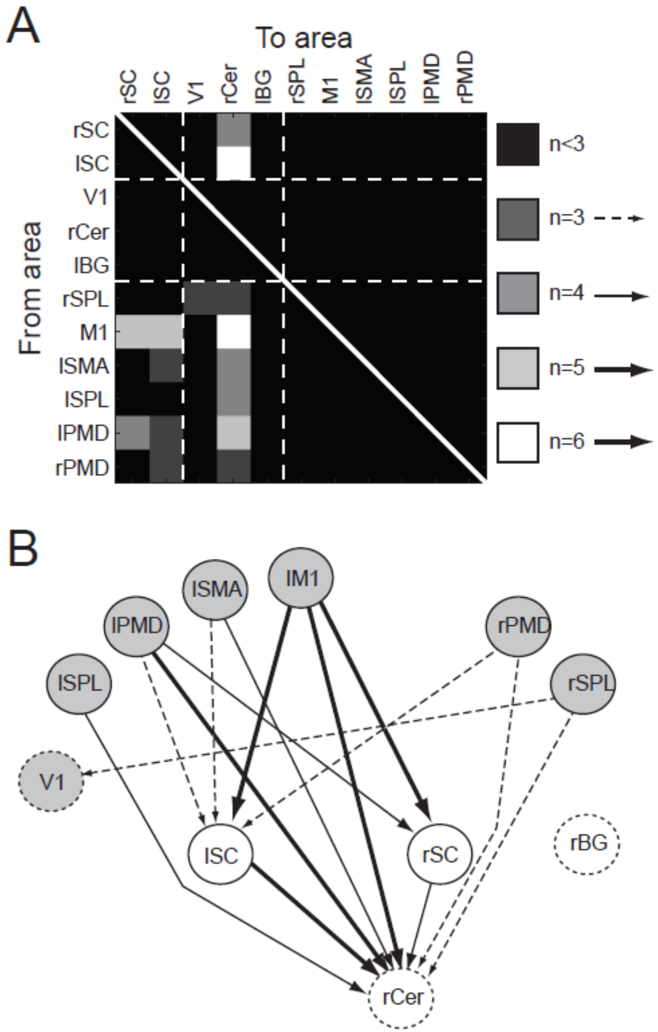
Cortical group with motor and pre-motor regions

Superior colliculi



# Directed structure (inferred by TE technique)

- Fewer region pairs had a significant directed relationship at the group level.
- We find an interesting hierarchical structure between the clusters.

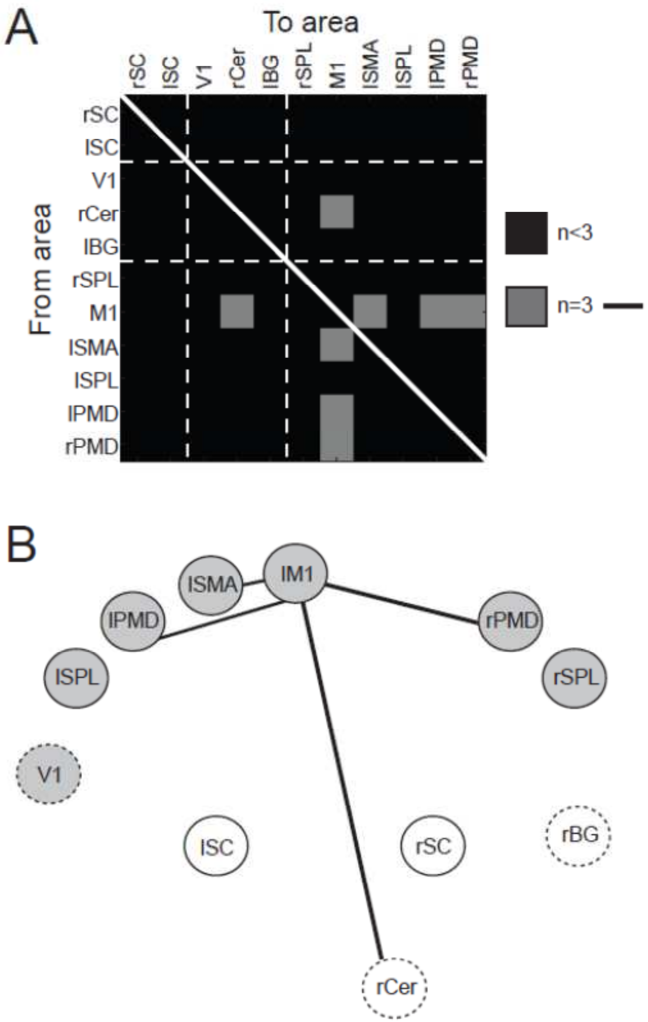



1. Structure correlates well to the experiment
2. Be aware of the influence of the measurement technique, e.g. low sampling rate may be responsible for no bottom-up links detected.

# Modulation of the undirected structure

- Increased coupling within the cortical cluster and from that cluster to motor execution

1. No significant modulation for directed structure: a change may be missed by the slow temporal resolution of the fMRI measurements.



# Final comments on the technique

- Numerical simulations show robustness to undersampling and memory in the data (akin to low-pass filtering in BOLD data)
- Our fMRI analysis was robust to the number of joint voxels *v* input to the multivariate analysis:
  - Structure shown for v=3 here is consistent for various multivariate v (suggests little high-dimensional multivariate interactions)
  - Univariate analysis (v = 1) is correlated but does not capture all structure.
- Use of average activity levels for the ROIs did not infer any interregional links at the group level $\rightarrow$ we need voxel level analysis.

# Conclusion

- Useful method for investigating interregional information structure demonstrated:
  - Satisfies several key requirements: explicitly measures information transfer, is directional, captures non-linear and collective interactions, works on a regional level, is robust to small data sets, distinguishes weak relationships from none, and is model-free.
- Technique verified using numerical data sets
- Technique inferred an interesting 3-tier inter-regional structure in fMRI data from a visuo-motor tracking task
- As task becomes more difficult, there is an increased coupling between regions involved in movement planning and execution

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# Thank you for your attention!

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# Information theory: the natural domain

- Shannon entropy $$H(X) = -\sum_{x \in \mathcal{X}} P(x) \log P(x)$$
- Joint entropy $$H(X,Y) = -\sum_{x \in \mathcal{X}} \sum_{y \in \mathcal{Y}} P(x,y) \log P(x,y)$$
- Conditional entropy $$H(Y|X) = \sum_{x \in \mathcal{X}} \sum_{y \in \mathcal{Y}} P(x,y) \ \log \frac{P(x)}{P(x,y)}$$
- Mutual information $$I(X;Y) = \sum_{x \in \mathcal{X}} \sum_{y \in \mathcal{Y}} P(x,y) \ \log \frac{P(x,y)}{P(x)P(y)}$$

$$I(X;Y) = H(X) + H(Y) - H(X,Y)$$

- Conditional mutual information $$I(X;Y|Z) = H(X|Z) - H(X|Y,Z)$$