Information theory in systems biology

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Learning from data

How biology learns?
(neuroscience, cog. sci., signaling, regulation)

How to analyze data?
(statistics, machine learning, data mining, bioinformatics)

Neural coding in H1

Regulation in B cells

Information theory
Studying signal transduction

Processor

Relation = I

What is the richness of ins/outs?
How faithful is the output to the input?
How does it coding input?
Studying signal transduction

What is the in/out relation?
Efficiency of estimation?
Efficiency of encoding?
Studying signal transduction

Synergies for multiple ins/outs?

What is I?
Reconstructing interaction models

\[ I(A,C) \leq \min[I(A,B), I(B,C)] \]

What is I?
Variances and Correlations

\[ \sigma^2(x) \]  
\[ \rho(x, x^2) = 0 \]

\[ \rho\left(f(x), g(y)\right) \neq \rho(x, y) \]  
not invariant

One-to-one transformations of microarray expression data completely destroys the ranking of correlations. Even sign of correlations may change.
Entropy (unique measure of randomness, in bits)

\[ S[X] = -\sum_{x=1}^{K} p_x \log p_x = -\langle \log p_x \rangle \]

\[ 0 \leq S[X] \leq \log K \quad \text{(number of “bins”)} \]

\[ N(x_0, \sigma^2) \Rightarrow S[X] = \frac{1}{2} \log(2\pi e\sigma^2) \]
Mutual Information
(interactions, shared data)

\[ I[X;Y] = \left\langle \log \frac{p_{xy}}{p_x p_y} \right\rangle \]

\[ = S[X] + S[Y] - S[X,Y] \]

\[ 0 \leq I[X;Y] \leq \min(S[X], S[Y]) \]

\[ N[(x_0, y_0), \Sigma] \Rightarrow I[X;Y] = -\frac{1}{2} \log(1 - \rho_{xy}^2) \]
Why MI?

- Captures all dependencies (zero iff joint probabilities factorize)
- Reparameterization invariant
- Unique metric-independent measure of “how related”

(Nemenman and Tishby 2005)
Why is IT not common in statistics?

Maximum likelihood estimation:

\[ S_{ML} = - \sum_i \frac{n_i}{N} \log \frac{n_i}{N} \]

\[ p_i^{ML} = \frac{n_i}{N} \]

(K - # of bins)

(N - sample size)

\[ \langle S_{ML} \rangle \leq - \sum_i \frac{\langle n_i \rangle}{N} \log \frac{\langle n_i \rangle}{N} = S \]
Why is IT not common in statistics?

$$\langle S_{ML} \rangle \leq - \sum_i \frac{\langle n_i \rangle}{N} \log \frac{\langle n_i \rangle}{N} = S$$

Fluctuations underestimate entropies and overestimate mutual informations.

(Need smoothing.)
Correct smoothing possible

\[ S \leq \log N \]

(often not enough)

Incorrect smoothing = over- or underestimation.

Developed for problems ranging from mathematical finance to computational biology.

For estimation of entropy at \( K / N \leq 1 \) see:

What if $S > \log N$?

But there is hope (Ma, 1981):

For uniform $K$-bin distribution the first coincidence occurs for

$$N_c \sim \sqrt{K} = \sqrt{2^S}$$

$$S \sim 2 \log N_c$$

Can make estimates for square-root-fewer samples!

Can this be extended to nonuniform cases?

- Assumptions needed (won’t work always)
- Estimate entropies without estimating distributions.
What is unknown?

Binomial distribution:

\[ S = -p \log p - (1 - p) \log(1 - p) \]

Assume (Bayes)

uniform (no assumptions)
Selection of wrong “unknown” biases the estimation.

(Even worse for large $K$.)
One possible uniformization strategy for $S$ (NSB)

- Posterior variance scales as $\frac{1}{\sqrt{N}}$
- Little bias, except in some known cases.
- Counts coincidences and works in Ma regime (if works).
- Is guaranteed correct for large $N$.
- Allows infinite # of bins.

If fails: What if we need only $S$ and $I$ ranks?
Now: apply all this to study neural coding

- Can we understand the code?
- Which features of it are important?
  - Is this a rate or a timing code?
- What/how much does the fly know?
- Is there an evidence for optimality?

Motion estimation is nontrivial and behaviorally important
Recording from fly’s H1

(Lewen et al, 2001)
Natural stimuli

- ~2 ms resolution known to be important for white noise stimuli
- Could such “brisk” spikes be due to ~1 ms correlations in stimulus?
- What if stimulus has natural correlations?

\[ \tau = 60 \text{ms} \]
\[ \text{response} = 30 \text{ms} \]
Natural stimulus and response
Highly repeatable spikes (not rate coding)

Is high precision timing for natural stimuli relevant for information transmission, or just anecdotal?
Analysis

- Collect joint samples of stimuli and responses
- No useful linear features observed
- Analyze $I(s,r)$
- Analyze $r$ up to 30-60 ms, at discretization up to 0.2 ms -- words up to 150 symbols
- Severely undersampled (100 to 10000 samples). Couldn’t be done before:

Use NSB!
Information rate at $T=30\text{ms}$

- Information present up to $\tau = 0.2-0.3 \text{ ms}$
- $30\%$ more information at $\tau < 1\text{ms}$. Encoding by refractoriness?
- $\sim 1\text{ bit/spike}$ at $170$ spikes/s and low-entropy correlated stimulus. Design principle?
- Efficiency $>50\%$ for $\tau > 1\text{ms}$, and $\sim 75\%$ at $30\text{ms}$. Optimized for natural statistics?

0.2 ms -- comparable to channel opening/closing noise and experimental noise.
Synergy from spike combinations

Redundancy due to stimulus

Spike pairs
New bits

- Spikes are very regular (15 oscillat.); decoding?
- Corr. Func. at half its value, but fly gets new bits every 30 ms
- Independent info (even though entropies are $T$ dependent).

Behaviorally optimized code!
Information about…

Signal shape

Best estimation at 25 ms delay. Little time for reaction.

Zero-crossings time
Same IT techniques needed (have been used) to study:

- Adaptation of the code to stimuli statistics (to maximize information transmission)
- Speed of adaptation
- Individuality of animals
- Effects of multiple neurons
- Predictive features selection by the fly
Reconstructing interaction networks

A: Small data requirements
   - Stat: ✖
   - Co: ✔
   - GM: ✔
   - Biochem.: ✖

B: Robustness to fluct.
   - Stat: ✔
   - Co: ✔
   - GM: ✖
   - Biochem.: ✖

C: Computational complexity
   - Stat: ✔
   - Co: ✔
   - GM: ✖
   - Biochem.: ✖

C: Conditional interactions
   - Stat: ✔
   - Co: ✖
   - GM: ✔
   - Biochem.: ✖

C: Reparam inv., non-param.
   - Stat: ✔
   - Co: ✔
   - GM: ✖
   - Biochem.: ✔

Irreducibility
   - Stat: ✔
   - Co: ✖
   - GM: ✔
   - Biochem.: ✖

I > 0

A

B

I > 0

C

What is an interaction in IT?
Two separate problems

- What is an interaction?
- Realistic algorithm to uncover them
Kullback-Leibler divergence

\[ D_{KL} [P \parallel Q] = \sum_x p_x \log \frac{p_x}{q_x} \]

\[ 0 \leq D_{KL} \]

How easy it is to mistake \( P \) for \( Q \)?
(KS test, etc.)
MI as MaxEnt

Find least constrained (highest entropy) approximation \( q \) to \( p_{xy} \), s.t.

\[
\begin{align*}
    p_x &= q_x \\
    p_y &= q_y \\
    q_{xy} &= \frac{1}{Z} \exp[-\varphi_x - \varphi_y] = p_x p_y
\end{align*}
\]

\[
I[X;Y] = D_{KL}[P \parallel Q]
\]
Higher order dependencies

\[ I_{XYZ} = \left\langle \log \frac{p_{xyz}}{p_x p_y p_z} \right\rangle \]

(Axiomatically) Amount of *all* dependencies (in bits) among variables.

But these are not irreducible.

(Nemenman and Tishby 2005)
By analogy:
Example of irreducibility

\[ P_{ABC} = \frac{P_{AB} P_{AC}}{P_A} = \frac{1}{Z} f_{AB} f_{BC} \]

MaxEnt approximation without BC:

\[ Q_{ABC} = \frac{1}{Z} \exp(-\varphi_{AB} - \varphi_{AC}) \quad \Rightarrow \quad D_{KL}[P_{ABC} \parallel Q_{ABC}] = 0 \]

No irreducible interaction!

For other links, e.g., AB:

\[ D_{KL}[P_{ABC} \parallel Q_{ABC}] > 0 \]

Irreducible interaction.
Higher order irreducible dependencies

How much dependency is there in a set of nodes that is not present in any of its subsets?

(Schneidman et al. 2003, Nemenman 2004)
MaxEnt approximations

\[ P_{12345} \]
MaxEnt approximations

\( P_{12346} \)
MaxEnt approximations

\[ P_{12456} \]
MaxEnt approximations

\[ Q = \frac{1}{Z} \exp\left[ -\varphi_{12345} - \varphi_{12346} - \varphi_{12456} \right] \]
MaxEnt approximations

\[ Q = \frac{1}{Z} \exp[-\varphi_{12345} - \varphi_{12346} - \varphi_{12456}] \]

\[ Q' = \frac{1}{Z} \exp[-\varphi_{12345} - \varphi_{12346} - \varphi_{12456} - \varphi_{356}] \]
MaxEnt approximations

\[ I_{356}' = D_{KL}[Q' \parallel Q] \]

\[ I_{356}' > 0 \Rightarrow \text{Irreducible interaction present} \]
MaxEnt factorization of PDFs

\[ P(x_1, \ldots x_M) = \]
\[ = \exp \left[ - \sum_i \varphi_i(x_i) - \sum_{ij} \varphi_{ij}(x_i, x_j) - \sum_{ijk} \varphi_{ijk}(x_i, x_j, x_k) - \cdots \right] \]

- \( N \)-particle potentials
- Spin models (for discrete variables)
- Random lattices
- Message passing
- Markov Networks
Two separate problems

- What is an interaction?
  An irreducible statistical dependency.

- Realistic algorithm to uncover them
  - Biologically sound assumptions (new knowledge from verifying assumptions).
  - Know the order.
  - Focus on high precision (irreducibility, no false positives), not so much on high recall (no false negatives).
Interaction network

(Basso et al. 2005, Margolin et al. 2005)
Disregard high orders (few data)
Locally tree-like approximation

$I_{34}$
Locally tree-like approximation

$I'_{34}$
Locally tree-like: signals decorrelate fast

\[ I_{34} \geq I'_{34} \]
ARACNE: No false positives
Where 2-way -- it’s 2-way

$I(A, C) \leq \min[I(A, B), I(B, C)]$

More care needed for loops of size 3

Techniques for MI estimation needed again!
\[
\frac{dx_i}{dt} = a_i \prod_j \frac{I_{0,j}^{\nu_j}}{I_j^{\nu_j} + I_{0,j}^{\nu_j}} \prod_j \left(1 + \frac{A_{0,j}^{\nu_j}}{A_j^{\nu_j} + A_{0,j}^{\nu_j}}\right) - b_i x_i
\]
Synthetic networks benchmarks ($N=1000$)

Graceful decay for smaller $N$
Complete B-cell network (400 arrays)

~129000 interactions
c-MYC subnetwork

- Protooncogene,
- 12% background binding,
- one of top 5% hubs
- significant MI with 2000 genes

Total interactions: 56
Pre-known: 22
Ch-IP validated: 11/12
Also validated in...

- Other hubs
- Various yeast data sets
- RBC metabolic network

~80% precision
20-80% recall (depending on N)
3rd order interactions
(modulated, conditional)

Nontranscriptional modulators!
Computational constraint: large modulators/hubs only
3rd order interactions

- Focus on important hubs (c-MYC)
- Pre-filter candidate modulators by dynamic range and other conditions.
- Find modulators whose expression inflicts large changes on hubs’ interactions
- No guarantee of irreducibility
- Validate in GO w.r.t. to transcription factors and kinases among modulators
c-MYC modulators

- 1117 candidate modulators (825 with known molecular function in GO)
- 82 (69) candidate modulators identified
- Kinases: 10/69 (backgr. 42/825), p=1e-3
- TFs: 15/69 (backgr. 56/825), p=1e-6; binding signature for co-TFs (E2F5, MEF2B) found.
- Total: 25/69 (backgr. 98/825), p=3e-8
- Other modulators: ubiquitin conjugating enzyme, mRNA stability, DNA/chromatin modification, known protein-protein target.
Many correlated modulators

|expression| change in interactions

Over 70% cluster overlap
Reducibility: modulating pathways

- **LYN**
- **FYN**
- **HCK**
- **BLNK**
- **AKT**
- **GSK3**
- **SYK**
- **Igα**
- **Igβ**
- **CD22**
- **BCR**
- **PLCγ**
- **PKC**
- **DAG**
- **IP3**
- **Ca^{2+}**
- **ERK**
- **JNK**
- **IKK**
- **NF-κB**
- **NFAT**
- **MYC**

- **predicted modulators**
- **not in the candidate list**
- **TF’s not predicted**
- **Protein complex**
- **Targets**
Currently

- Biochemical validation
- Search for irreducible modulators
Summary

- IT quantities better measures of dependency
- **Problem:** estimation. **Solutions:** NSB (“don’t know” about entropies), stability of ranks
- **Application:** analysis of neural code at high resolution. **Found:** timing code, synergy, redundancy removal, photon counting -- optimality?
- **Problems:** what is an irreducible interaction? Algorithms with controlled approximations? **Solutions:** MaxEnt approximations, ARACNE, conditional ARACNE
- **Application:** B-cells microarrays analysis. **Found:** great performance on synthetic data, c-MYC targets (high precision validation), c-MYC modulators (to be validated, many confirmed by literature)
Thanks

- Columbia: Andrea Califano, Adam Margolin, Kai Wang, Nila Banerjee, Omar Antar, Riccardo Dalla-Favera, Katia Basso, Chris Wiggins, AMDeC
- IBM: Gustavo Stolovitzky
- Princeton: William Bialek, Fariel Shafee
- Indiana: Rob de Ruyter van Steveninck
- Jerusalem: Naftali Tishby
- OSDN/SourceForge