Discovery of Gene Regulatory Networks Using Adaptively Selected Perturbation Experiments

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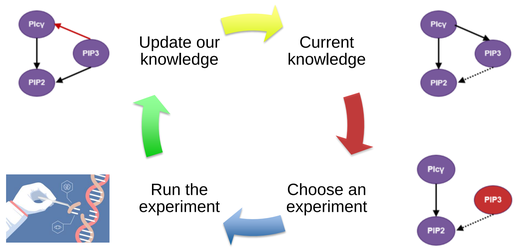
Objective

To build an adaptive learning algorithm for inferring gene networks by iterating between experimentation and analysis.



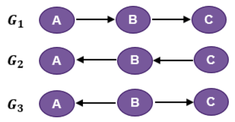
Background

Representing the network

- Causal Bayesian network (directed acyclic graph)
- Nodes: random variables representing gene expression values
- Edges: causal, regulatory relationships

Markov equivalence classes

- Networks that represent the same set of dependencies and conditional independencies, e.g.



Benefit of perturbation data

- Observational data alone cannot distinguish among networks in the same equivalence class.
- Perturbing node A affects descendants of A, allowing us to distinguish $\{G_1\}$ from $\{G_2, G_3\}$.

Entropy as a measure of uncertainty

- Three possible edge relationships for two nodes: $A \rightarrow B$, $A \leftarrow B$, and $A \perp B$.

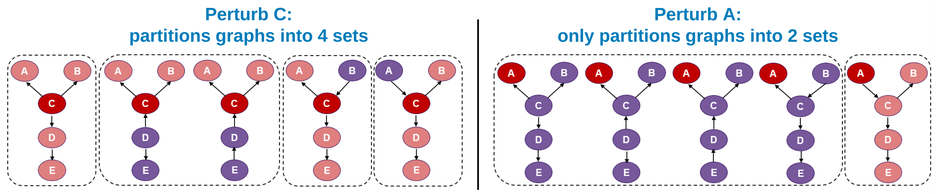
- Tong and Koller (2001) define edge entropy as:

$$H(A \leftrightarrow B) = -P(A \rightarrow B)\ log\ P(A \rightarrow B) - P(A \leftarrow B)\ log\ P(A \leftarrow B) - P(A \perp B)\ log\ P(A \perp B)$$

- The larger this entropy, the less certain we are about the relationship between A and B.

Selection Criterion

Motivation: perturb the node whose descendant sets are maximally different.



- Sampling variability leads to uncertainty in the descendant set partitions.
- Capture uncertainty of whether node B is a descendant of A, $d(A)$, via:

$$H\big(B \in d(A)\big) = -P\big(B \in d(A)\big) * log\ P\big(B \in d(A)\big) - \big([1 - P\big(B \in d(A)\big)] * log[1 - P\big(B \in d(A)\big)]\big)$$

$P\big(B \in d(A)\big)$ **is calculated empirically from graphs sampled from the posterior on graphs G given data D:**

$$P(B \in d(A)|D) = \sum_{[B \in d(A)] \in G} P(G|D)$$

Descendant entropy: captures the overall uncertainty in the descendants of A.

$H(A) = \sum_j H\big(j \in d(A)\big)$ **for all nodes j in $G \backslash A$**

- Greatest information gain achieved by perturbing the node with the largest descendant entropy.

- "Adaptive descendant" method uses descendant entropy as the criterion; substitute $d(A)$ with $c(A)$ to compare with the "adaptive child" method.

Adaptive Learning Algorithm

1. Sample n_{obs} instances from the ground truth Bayesian network.

2. Use MCMC to obtain posterior samples from $P(G \mid D)$.
   - Metropolis-Hastings proposals with an edge addition, deletion, or reversal.

3. Calculate $P\big(B \in d(A)\big)$ and $H\big(B \in d(A)\big)$ empirically from the sampled graphs for all node pairs.

4. Check the stop criterion. Continue performing experiments until either:
   - minimum desired entropy is achieved
   - maximum number of allowed experiments is reached

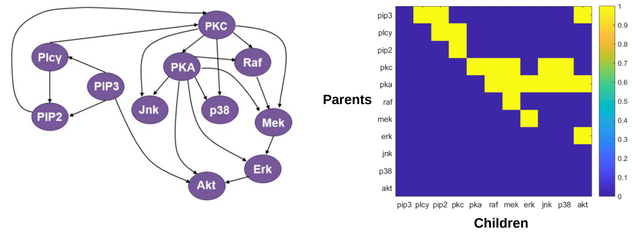
5. Select $arg\ max_{\{A \in T\}} H(A)$ as the next node to perturb.
   - T: set of nodes eligible for interventions.

6. Generate n_{pert} instances from the Bayesian network.

7. Combine the new data with the existing data and return to step 2.

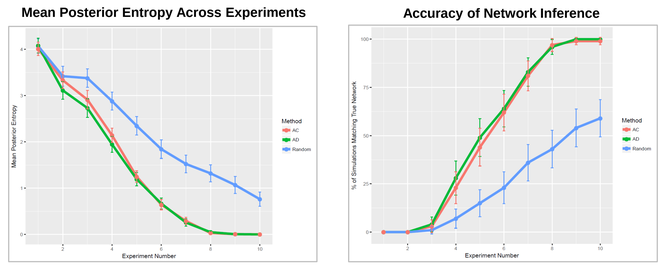
Results

Protein-signaling network used to simulate gene expression data, adapted from Sachs et al. (2005):

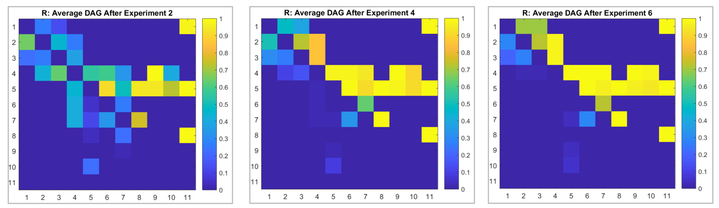


The adaptive descendant (AD) and adaptive child (AC) methods outperform random (R) node selection, as evidenced by:

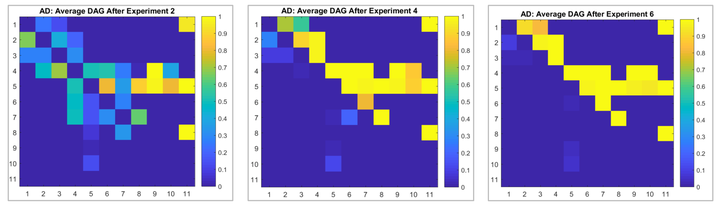
(1) faster rates of entropy reduction, and
(2) greater accuracy in inferring the true causal network.



Random Node Selection



Adaptive Descendant Node Selection



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