Reconstructing gene regulatory networks with Bayesian networks by combining gene expression profiles with multiple sources of prior knowledge

Dirk Husmeier
Reconstructing Gene Regulatory Networks with Bayesian Networks by Combining Expression Data with Multiple Sources of Prior Knowledge

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Bayesian inference

Select the model \( M \) based on the posterior probability:

\[
P(M|D) \propto P(D|M)P(M)
\]

This requires an integration over the whole parameter space:

\[
P(D|M) = \int P(D|q, M)P(q|M) dq
\]
Uncertainty about the best network structure

Limited number of experimental replications, high noise

$P(\mathcal{D}|\mathcal{M})$
Reduced uncertainty by using prior knowledge

\[ P(\mathcal{M}|\mathcal{D}) \propto P(\mathcal{D}|\mathcal{M})P(\mathcal{M}) \]
• Which sources of prior knowledge are reliable?
• How do we trade off the different sources of prior knowledge against each other and against the data?
Estimating gene networks from gene expression data by combining Bayesian network model with promoter element detection

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Use TF binding motifs in promoter sequences
**Biological Prior Knowledge**

Biological prior knowledge matrix

\[
P = \begin{pmatrix}
p_{11} & p_{12} & p_{13} & \cdots & p_{1n} \\
p_{21} & p_{22} & p_{23} & \cdots & p_{2n} \\
p_{31} & p_{32} & p_{33} & \cdots & p_{3n} \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
p_{n1} & p_{n2} & p_{n3} & \cdots & p_{nn}
\end{pmatrix}
\]

\[0 \leq p_{ij} \leq 1\]

\[p_{ij}\] Indicates some knowledge about the relationship between genes \(i\) and \(j\).

---

Define the energy of a Graph \(G\)

\[
g_{ij} \in \{0, 1\}
\]

\[
G = \begin{pmatrix}
g_{11} & g_{12} & g_{13} & \cdots & g_{1n} \\
g_{21} & g_{22} & g_{23} & \cdots & g_{2n} \\
g_{31} & g_{32} & g_{33} & \cdots & g_{3n} \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
g_{n1} & g_{n2} & g_{n3} & \cdots & g_{nn}
\end{pmatrix}
\]

\[E(G) = \sum_{i,j=1}^{n} |P_{i,j} - G_{i,j}|\]
Prior knowledge

“I don’t know”

“I’m sure about this”
Prior probabilities

P = 0.5

P = 1.0
“Prior probabilities”

$P=0.5$

$P=1.0$

Network structures for independent edges

$P=0$

$\sum P = 1$

$P=0.5$
“Prior probabilities”

P=0.5

DAG structures

P=1.0

Invalid
“Prior probabilities”

P=0.5

P=0

P=0.5

P=1.0

P=1.0

DAG structures
Prior probabilities

DAG structures

P = 0.5

P = 0

P = 0.5

P = 1.0

Σ P = 1.5 ≠ 1.0

Not a probability distribution
“Prior probabilities”

DAG structures

P=0.5  

P=0

P=0.5

P=1.0

Σ P = 1.5 ≠ 1.0

Not a probability distribution

Obtaining a proper probability distribution in DAG space requires a renormalization
Notation

• Prior knowledge matrix:
  $P \rightarrow B$ (for “belief”)

• Network structure:
  $G$ (for “graph”) or $M$ (for “model”)

• $P$: Probabilities
Deviation between the network \( G \) and the prior knowledge \( B \):

\[
E(G) = \sum_{i,j=1}^{N} |B_{i,j} - G_{i,j}|
\]

"Energy"

Prior distribution over networks

\[
P(G|\beta) = \frac{e^{-\beta E(G)}}{Z(\beta)}
\]

\[
Z(\beta) = \sum_{G \in G} e^{-\beta E(G)}
\]

Graph: \( \in \{0,1\} \)

Prior knowledge: \( \in [0,1] \)

Hyperparameter
Bayesian analysis: integration of prior knowledge

Hyperparameter $\beta$ trades off data versus prior knowledge

Microarray data

KEGG pathway
Hyperparameter $\beta$ trades off data versus prior knowledge.

Microarray data

$\beta$ small

KEGG pathway
Hyperparameter $\beta$ trades off data versus prior knowledge.

Microarray data

KEGG pathway
New contribution

• Generalisation to more sources of prior knowledge
• Inferring the hyperparameters
• Bayesian approach
Multiple sources of prior knowledge

\[ E_1(G) = \sum_{i,j=1}^{N} |B_{i,j}^{1} - G_{i,j}| \]

\[ E_2(G) = \sum_{i,j=1}^{N} |B_{i,j}^{2} - G_{i,j}| \]

\[ P(G|\beta_1, \beta_2) = \frac{e^{-\{\beta_1 E_1(G) + \beta_2 E_2(G)\}}}{Z(\beta_1, \beta_2)} \]

\[ Z(\beta_1, \beta_2) = \sum_{G \in G} e^{-\{\beta_1 E_1(G) + \beta_2 E_2(G)\}} \]
Input: $D$

Learn: $M$

$\beta, M \sim P(\beta, M | D, B)$
Sample networks and hyperparameters from the posterior distribution

\[ P(G, \beta_1, \beta_2 | D) \]

Proposal probabilities

\[ Q(G_{new} | G_{old}) \]
\[ R(\beta_{1_{new}} | \beta_{1_{old}}) \]
\[ R(\beta_{2_{new}} | \beta_{2_{old}}) \]

Metropolis-Hastings scheme
Sample networks and hyperparameters from the posterior distribution

\[ P(G, \beta_1, \beta_2 | D) \]

Proposal probabilities

\[ Q(G_{\text{new}} | G_{\text{old}}) \]

\[ R(\beta_{1,\text{new}} | \beta_{1,\text{old}}) \quad R(\beta_{2,\text{new}} | \beta_{2,\text{old}}) \]

Metropolis-Hastings scheme

\[
A = \min \left\{ \frac{P(D, G_{\text{new}}, \beta_{1,\text{new}}, \beta_{2,\text{new}}) Q(G_{\text{old}} | G_{\text{new}}) R(\beta_{1,\text{old}} | \beta_{1,\text{new}}) R(\beta_{2,\text{old}} | \beta_{2,\text{new}})}{P(D, G_{\text{old}}, \beta_{1,\text{old}}, \beta_{2,\text{old}}) Q(G_{\text{new}} | G_{\text{old}}) R(\beta_{1,\text{new}} | \beta_{1,\text{old}}) R(\beta_{2,\text{new}} | \beta_{2,\text{old}})}, 1 \right\}
\]
Bayesian networks with two sources of prior

Source 1 → BNs + MCMC → Source 2

Data

Recovered Networks and trade off parameters
Bayesian networks with two sources of prior

Source 1 ➔ Data ➔ BNs + MCMC ➔Recovered Networks and trade off parameters ➔ Source 2

\[ \beta_1 \] 

\[ \beta_2 \]
Bayesian networks with two sources of prior

Source 1 → Data → BNs + MCMC → Recovered Networks and trade off parameters → Source 2

\( \beta_1 \) \( \beta_2 \)
Sample networks and hyperparameters from the posterior distribution

\[ P(G, \beta_1, \beta_2 | D) \]

Proposal probabilities

\[ Q\left( G_{\text{new}} | G_{\text{old}} \right) \]

\[ R\left( \beta_{1_{\text{new}}} | \beta_{1_{\text{old}}} \right) \quad R\left( \beta_{2_{\text{new}}} | \beta_{2_{\text{old}}} \right) \]

Metropolis-Hastings scheme

\[
A = \min \left\{ \frac{P(D, G_{\text{new}}, \beta_{1_{\text{new}}}, \beta_{2_{\text{new}}}) Q(G_{\text{old}} | G_{\text{new}}) R(\beta_{1_{\text{old}}} | \beta_{1_{\text{new}}}) R(\beta_{2_{\text{old}}} | \beta_{2_{\text{new}}})}{P(D, G_{\text{old}}, \beta_{1_{\text{old}}}, \beta_{2_{\text{old}}}) Q(G_{\text{new}} | G_{\text{old}}) R(\beta_{1_{\text{new}}} | \beta_{1_{\text{old}}}) R(\beta_{2_{\text{new}}} | \beta_{2_{\text{old}}})}, 1 \right\}
\]

\[
A = \min \left\{ \frac{P(D | G_{\text{new}}) P(G_{\text{new}} | \beta_{1_{\text{new}}}, \beta_{2_{\text{new}}}) P_1(\beta_{1_{\text{new}}}) P_2(\beta_{2_{\text{new}}})}{P(D | G_{\text{old}}) P(G_{\text{old}} | \beta_{1_{\text{old}}}, \beta_{2_{\text{old}}}) P_1(\beta_{1_{\text{old}}}) P_2(\beta_{2_{\text{old}}})} \times \right. \frac{Q(G_{\text{old}} | G_{\text{new}}) R_1(\beta_{1_{\text{old}}} | \beta_{1_{\text{new}}}) R_2(\beta_{2_{\text{old}}} | \beta_{2_{\text{new}}})}{Q(G_{\text{new}} | G_{\text{old}}) R_1(\beta_{1_{\text{new}}} | \beta_{1_{\text{old}}}) R_2(\beta_{2_{\text{new}}} | \beta_{2_{\text{old}}})}, 1 \right\}
\]
Sample networks and hyperparameters from the posterior distribution

\[ P(G, \beta_1, \beta_2 | D) \]

Proposal probabilities

\[ Q(G_{\text{new}} | G_{\text{old}}) \quad R(\beta_{1\text{new}} | \beta_{1\text{old}}) \quad R(\beta_{2\text{new}} | \beta_{2\text{old}}) \]

Metropolis-Hastings scheme

\[
A = \min \left\{ \frac{P(D, G_{\text{new}}, \beta_{1\text{new}}, \beta_{2\text{new}}) Q(G_{\text{old}} | G_{\text{new}}) R(\beta_{1\text{old}} | \beta_{1\text{new}}) R(\beta_{2\text{old}} | \beta_{2\text{new}})}{P(D, G_{\text{old}}, \beta_{1\text{old}}, \beta_{2\text{old}}) Q(G_{\text{new}} | G_{\text{old}}) R(\beta_{1\text{new}} | \beta_{1\text{old}}) R(\beta_{2\text{new}} | \beta_{2\text{old}})} , 1 \right\}
\]

\[
A = \min \left\{ \frac{P(D | G_{\text{new}}) P(G_{\text{new}} | \beta_{1\text{new}}, \beta_{2\text{new}})}{P(D | G_{\text{old}}) P(G_{\text{old}} | \beta_{1\text{old}}, \beta_{2\text{old}})} , 1 \right\}
\]
Prior distribution

\[ E_1(G) = \sum_{i,j=1}^{N} |B_{i,j}^1 - G_{i,j}| \]

\[ E_2(G) = \sum_{i,j=1}^{N} |B_{i,j}^2 - G_{i,j}| \]

\[ P(G|\beta_1, \beta_2) = \frac{e^{-\{\beta_1 E_1(G) + \beta_2 E_2(G)\}}}{Z(\beta_1, \beta_2)} \]

\[ Z(\beta_1, \beta_2) = \sum_{G \in G} e^{-\{\beta_1 E_1(G) + \beta_2 E_2(G)\}} \]
Approximation of $Z$

$$E(G) = \sum_{i,j=1}^{N} |B_{i,j} - G_{i,j}|$$

Rewriting the energy

$$E(G) = \sum_{n=1}^{N} \mathcal{E}(n, \pi_n [G])$$

$$\mathcal{E}(n, \pi_n) = \sum_{i \in \pi_n} (1 - B_{in}) + \sum_{i \notin \pi_n} B_{in}$$
Approximation of the partition function

\[ Z = \sum_{G \in \mathcal{G}} e^{-\beta E(G)} \]

\[ = \sum_{\pi_1} \cdots \sum_{\pi_N} e^{-\beta (\mathcal{E}(1, \pi_1) + \cdots + \mathcal{E}(N, \pi_N))} \]

\[ = \prod_{n} \sum_{\pi_n} e^{-\beta \mathcal{E}(n, \pi_n)} \]

Partition function of an ideal gas
Individual partition functions

DAG structures

Invalid
Multiple sources of prior knowledge

\[ E_1(G) = \sum_{i,j=1}^{N} |B_{i,j}^1 - G_{i,j}| \]

\[ E_2(G) = \sum_{i,j=1}^{N} |B_{i,j}^2 - G_{i,j}| \]

\[ P(G|\beta_1, \beta_2) = \frac{e^{-\{\beta_1 E_1(G) + \beta_2 E_2(G)\}}}{Z(\beta_1, \beta_2)} \]

\[ Z(\beta_1, \beta_2) = \sum_{G\in \mathcal{G}} e^{-\{\beta_1 E_1(G) + \beta_2 E_2(G)\}} \]
Energy of a network

\[ E_1(G) = \sum_{n=1}^{N} E_1(n, \pi_n [G]) \]

\[ E_2(G) = \sum_{n=1}^{N} E_2(n, \pi_n [G]) \]

Rewriting the energy

\[ E_1(n, \pi_n) = \sum_{i \in \pi_n} (1 - B^1_{in}) + \sum_{i \notin \pi_n} B^1_{in} \]

\[ E_2(n, \pi_n) = \sum_{i \in \pi_n} (1 - B^2_{in}) + \sum_{i \notin \pi_n} B^2_{in} \]
Approximation of the partition function

\[ Z = \sum_{G \in \mathcal{G}} e^{-\{\beta_1 E_1(G)+\beta_2 E_2(G)\}} \]

\[ = \sum_{\pi_1} \cdots \sum_{\pi_N} e^{-\{\beta_1 [\mathcal{E}_1(1, \pi_1) + \ldots + \mathcal{E}_1(N, \pi_N)] + \beta_2 [\mathcal{E}_2(1, \pi_1) + \ldots + \mathcal{E}_2(N, \pi_N)]\}} \]

\[ = \prod_{n} \sum_{\pi_n} e^{-\{\beta_1 \mathcal{E}_1(n, \pi_n) + \beta_2 \mathcal{E}_2(n, \pi_n)\}} \]

Partition function of an ideal gas
Evaluation

• Can the method automatically evaluate how useful the different sources of prior knowledge are?
• Do we get an improvement in the regulatory network reconstruction?
• Is this improvement optimal?
Evaluation on the Raf regulatory network

From Sachs et al Science 2005
Raf signalling pathway

From Sachs et al Science 2005
Evaluation: Raf signalling pathway

- Cellular signalling network of 11 phosphorylated proteins and phospholipids in human immune systems cell
- Deregulation $\rightarrow$ carcinogenesis
- Extensively studied in the literature $\rightarrow$ gold standard network
Data
Prior knowledge
Flow cytometry data

• Intracellular multicolour flow cytometry experiments: concentrations of 11 proteins

• 5400 cells have been measured under 9 different cellular conditions (cues)

• Downsampling to 100 instances (5 separate subsets): indicative of microarray experiments
Microarray example

Cell cycle
73 samples

Tu et al (2005)
Metabolic cycle
36 samples
Data
Prior knowledge
Prior knowledge from KEGG
Prior distribution

\[ P(G|\beta) = \frac{e^{-\beta E(G)}}{Z(\beta)} \quad \text{and} \quad E(G) = \sum_{i,j=1}^{N} |B_{i,j} - G_{i,j}| \]

Define by \( M_{ij} \) the total number of times a pair of genes \( i \) and \( j \) appears in a pathway, and by \( m_{ij} \) the number of times the genes are connected by a (directed) edge in the KEGG pathway. The elements \( B_{ij} \) of the prior knowledge matrix are then defined by

\[ B_{ij} = \frac{m_{ij}}{M_{ij}} \quad (43) \]

If a pair of genes is not found in any of the KEGG pathways, we set the respective prior association to \( B_{ij} = 0.5 \), implying that we have no information about this relationship.
Prior knowledge from KEGG

Data: protein concentrations from flow cytometry experiments
Data and prior knowledge

Causal Protein-Signaling Networks Derived from Multiparameter Single-Cell Data

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A 1. Perturbations
   • Condition ‘a’
   • Condition ‘b’
   • Condition... ‘n’

2. Multiparameter Flow Cytometry

3. Correlated phospho-measures per cell

4. Datasets of cells
   • condition ‘a’
   • condition ‘b’
   • condition... ‘n’

5. Bayesian network analysis

6. Influence diagram of measured variables

+ KEGG
+ Random
Evaluation

• Can the method automatically evaluate how useful the different sources of prior knowledge are?
• Do we get an improvement in the regulatory network reconstruction?
• Is this improvement optimal?
Sampled values of the hyperparameters
Bayesian networks with two sources of prior knowledge

Random

Data

KEGG

BNs + MCMC

Recovered Networks and trade off parameters

$\beta_1$

$\beta_2$
Bayesian networks with two sources of prior knowledge

Random

Data

KEGG

BNs + MCMC

Recovered Networks and trade off parameters

$\beta_1$

$\beta_2$
Evaluation

• Can the method automatically evaluate how useful the different sources of prior knowledge are?

• **Do we get an improvement in the regulatory network reconstruction?**

• Is this improvement optimal?
Gold-standard network  Inferred network

Deterministic inference
Sample of high-scoring networks

$P(\mathcal{M}|\mathcal{D})$
Sample of high-scoring networks

Feature extraction, e.g. marginal posterior probabilities of the edges

High-confident edge

High-confident non-edge

Uncertainty about edges
Gold standard network

Inferred network distribution

Probabilistic inference
Gold-standard network

Thresholding

True positives  False positives
From Perry Sprawls

AUC: area under the curve

TPFP5: Sensitivity for 95% specificity
Evaluation

Two ways of interpreting edges

- **UGE**: undirected graph evaluation
- **DGE**: directed graph evaluation

Two evaluation procedures:

- **AUC**: Area under the ROC curve, with larger areas indicating, overall, a better performance.
- **TP count**: True positive number of edges for the same false positive count of FP=5 across all methods.
Flow cytometry data and KEGG
Evaluation

• Can the method automatically evaluate how useful the different sources of prior knowledge are?
• Do we get an improvement in the regulatory network reconstruction?
• Is this improvement optimal?
Learning the trade-off hyperparameter

- Repeat MCMC simulations for large set of fixed hyperparameters $\beta$
- Obtain AUC scores for each value of $\beta$
- Compare with the proposed scheme in which $\beta$ is automatically inferred.
Conclusions – Part 1

- The method can automatically evaluate how useful the different sources of prior knowledge are.
- We get an improvement in the regulatory network reconstruction.
- The improvement is close to optimal.
Part 2

Combining data from different experimental conditions
GENE REGULATORY NETWORK RECONSTRUCTION
BY BAYESIAN INTEGRATION OF PRIOR KNOWLEDGE
AND/OR DIFFERENT EXPERIMENTAL CONDITIONS

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What if we have multiple data sets obtained under different experimental conditions?

Example: Cytokine network

- Infection
- Treatment with IFN
- Infection and treatment with IFN
Monolithic

data data data data

Individual

data data data
Propose a compromise between the two
Compromise between the two previous ways of combining the data
\[ P(\mathcal{M}_1, \ldots, \mathcal{M}_I, \mathcal{D}_1 \ldots \mathcal{D}_I, \beta_1, \ldots, \beta_I, \mathcal{M}^*) = \prod_{i=1}^{I} P(\mathcal{D}_i | \mathcal{M}_i) P(\mathcal{M}_i | \beta_i, \mathcal{M}^*) P(\beta_i) P(\mathcal{M}^*) \]
\[ P(\mathcal{M}_1, \ldots, \mathcal{M}_I, \mathcal{D}_1 \ldots \mathcal{D}_I, \beta_1, \ldots, \beta_I, \mathcal{M}^*) = \prod_{i=1}^{I} P(\mathcal{D}_i|\mathcal{M}_i) P(\mathcal{M}_i|\beta_i, \mathcal{M}^*) P(\beta_i) P(\mathcal{M}^*) \]
\[ P(\mathcal{M}_1, \ldots, \mathcal{M}_I, \mathcal{D}_1 \ldots \mathcal{D}_I, \beta_1, \ldots, \beta_I, \mathcal{M}^*) = \prod_{i=1}^{I} P(\mathcal{D}_i | \mathcal{M}_i) P(\mathcal{M}_i | \beta_i, \mathcal{M}^*) P(\beta_i) P(\mathcal{M}^*) \]

\[ P(\mathcal{M}_i | \beta_i, \mathcal{M}^*) = \frac{e^{-\beta_i(|\mathcal{M}_i - \mathcal{M}^*|)}}{Z(\beta_i, \mathcal{M}^*)} \]
\[ P(\mathcal{M}_1, \ldots, \mathcal{M}_I, \mathcal{D}_1 \ldots \mathcal{D}_I, \beta_1, \ldots, \beta_I, \mathcal{M}^*) = \prod_{i=1}^I P(\mathcal{D}_i | \mathcal{M}_i) P(\mathcal{M}_i | \beta_i, \mathcal{M}^*) P(\beta_i) P(\mathcal{M}^*) \]

\[ Z(\beta, \mathcal{M}^*) = \sum_{\mathcal{M}_i \in \mathcal{M}} e^{-\beta_i(|\mathcal{M}_i - \mathcal{M}^*|)} \]

\[ P(\mathcal{M}_i | \beta_i, \mathcal{M}^*) = \frac{e^{-\beta_i(|\mathcal{M}_i - \mathcal{M}^*|)}}{Z(\beta, \mathcal{M}^*)} \]
\[ P(\mathcal{M}_1, \ldots, \mathcal{M}_I, \mathcal{D}_1 \ldots \mathcal{D}_I, \beta_1, \ldots, \beta_I, \mathcal{M}^*) = \prod_{i=1}^{I} \frac{P(\mathcal{D}_i | \mathcal{M}_i)P(\mathcal{M}_i | \beta_i, \mathcal{M}^*)P(\beta_i)P(\mathcal{M}^*)}{P(\mathcal{D}_i | \mathcal{M}_i)P(\mathcal{M}_i | \beta_i, \mathcal{M}^*)P(\beta_i)} \]

\[ Z(\beta_i, \mathcal{M}^*) = \sum_{\mathcal{M}_i \in \mathcal{M}} e^{-\beta_i(|\mathcal{M}_i - \mathcal{M}^*|)} \]

\[ = \prod_n \sum_{\pi_{\mathcal{M}}(n)} e^{-\beta E(n, \pi_{\mathcal{M}}(n))} \]

Ideal gas approximation
\[
A(M_{i\text{new}} | M_{i\text{old}}) = \min \left\{ \frac{P(D_i | M_{i\text{new}}) P(M_{i\text{new}} | \beta_i, M^*) Q_i(M_{i\text{old}} | M_{i\text{new}})}{P(D_i | M_{i\text{old}}) P(M_{i\text{old}} | \beta_i, M^*) Q_i(M_{i\text{new}} | M_{i\text{old}})}, 1 \right\}
\]

\[
A(\beta_{i\text{new}} | \beta_{i\text{old}}) = \min \left\{ \frac{P(M_i | \beta_{i\text{new}}, M^*)}{P(M_i | \beta_{i\text{old}}, M^*)}, 1 \right\}
\]

\[
A(M_{i\text{new}}^* | M_{i\text{old}}^*) = \min \left\{ \prod_{i=1}^{I} \frac{P(M_i | \beta_i, M_{i\text{new}}^*)}{P(M_i | \beta_i, M_{i\text{old}}^*)}, 1 \right\}
\]
Empirical evaluation

Real application: macrophages infected with CMV and pre-treated with IFN-γ

No gold-standard

Simulated data from the Raf signalling network
Simulated data

Raf network
Simulated data
Simulated data

v-Raf network
Simulated data

Raf network

v-Raf network
Simulated data

\[ X_i \sim N\left( \sum_k w_{ik} x_k, \sigma \right) \]

\[ \sigma = 0.1 \]

\[ |w_{ik}| \text{ uniform distribution over the interval } [0.5, 2] \]
Simulated Data

Weights between nodes are different for different data sets.
Simulated Data

Weights between nodes are different for different data sets.
5 data sets

100 data points each

1 random data set (pure noise)

1 data set from the modified network

3 data sets from the Raf network, but with different regulations strengths
Corrupt, noisy data

Modified network

Raf network
Evaluation of the network reconstruction performance

- We use the Area Under the Receiver Operating Characteristic Curve (ROC).

- ROC curves:
  - Random predictor: AUC=0.5
  - Perfect predictor: AUC=1
  - Realistic predictor: AUC=0.75
Simulated data

AUC

- monolithic
- uncoupled
- coupled

DGE
UGE
Thank you!

Any questions?