College of Science - Department of Statistics
Statistical Bioinformatics Center

Reverse Engineering Gene Networks Using Approximate Bayesian Computation (ABC)

Rencontre de statistique autour des modèles hiérarchiques: Université de Strasbourg

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January 14, 2011

Outline

1. Introduction
   - Gene regulatory networks
2. Approximate Bayesian Computation
   - Background and motivation
   - Monte Carlo approaches
3. ABC-MCMC for Networks
   - Simulation studies
   - Real data analysis: SOS DNA repair system in *E. coli*
4. Discussion

Gene Expression

- Genes: Functional regions of DNA that encode proteins and RNA molecules

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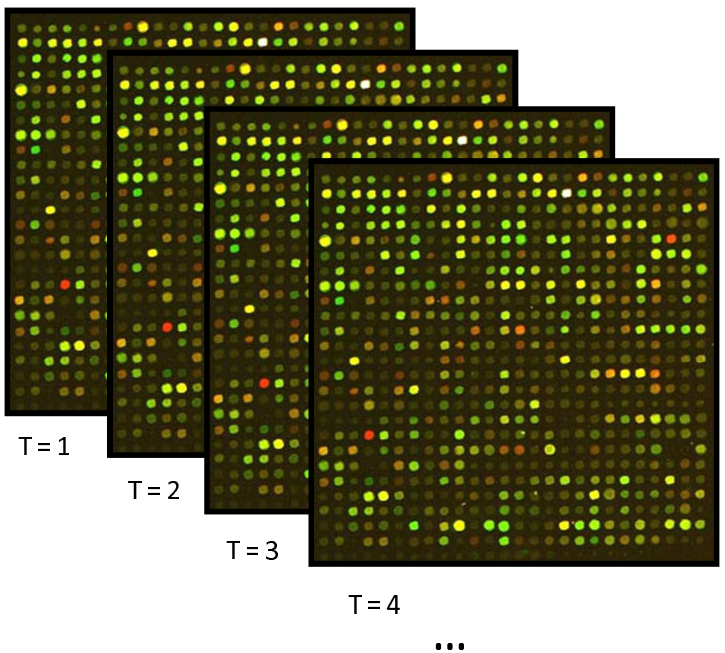
- Expression levels of thousands of genes can be measured using "high-throughput" technologies (e.g., microarrays, serial analysis of gene expression, next-generation sequencing)

Time-Course Gene Expression

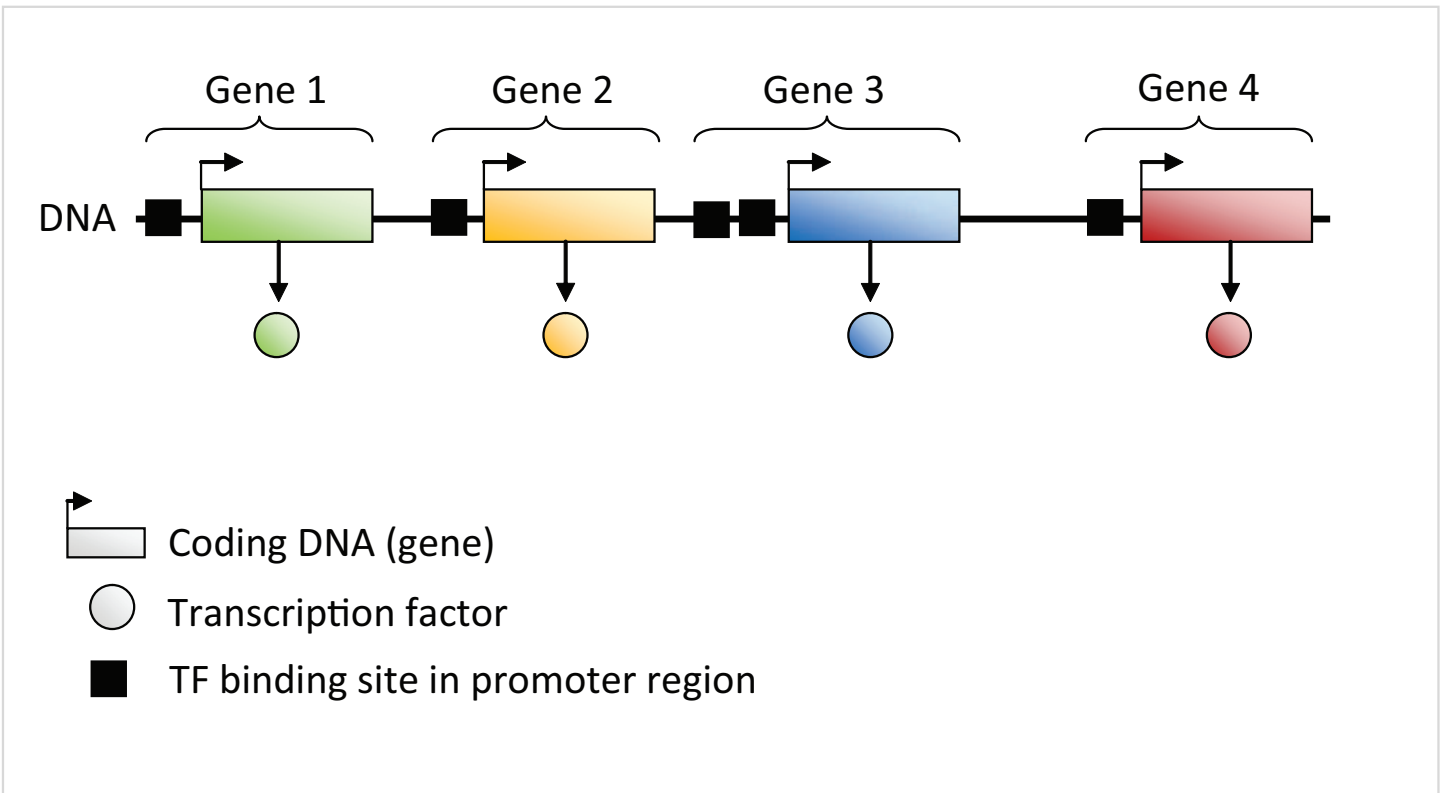
- Time-course gene expression data can elucidate information about *patterns* of relationships of gene expression in a cell



- Large number of genes, few biological replicates or time points... $N \ll P$ paradigm

Gene Regulatory Networks

- *Gene regulatory networks*: set of genes that interact indirectly with one another through proteins called transcription factors (TF)



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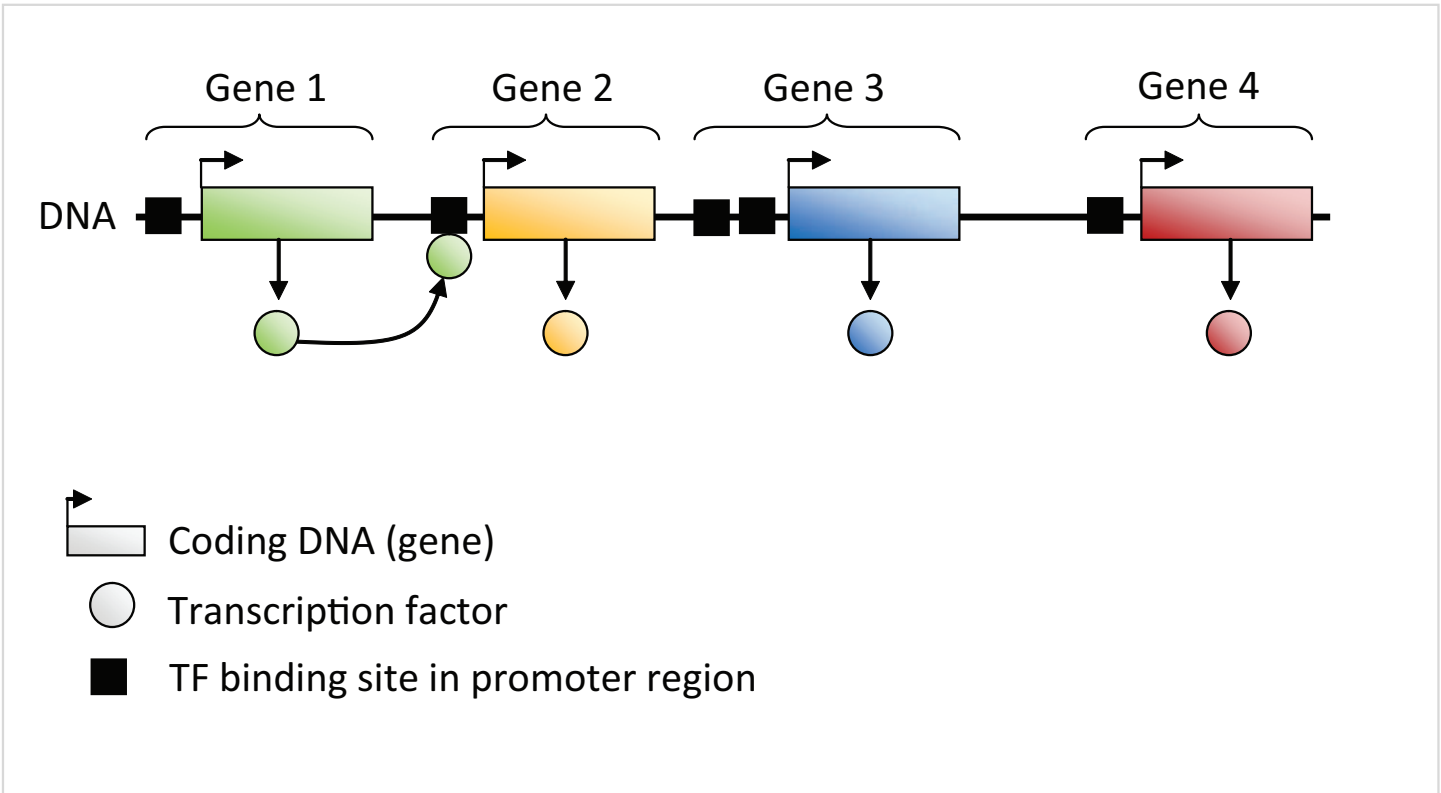

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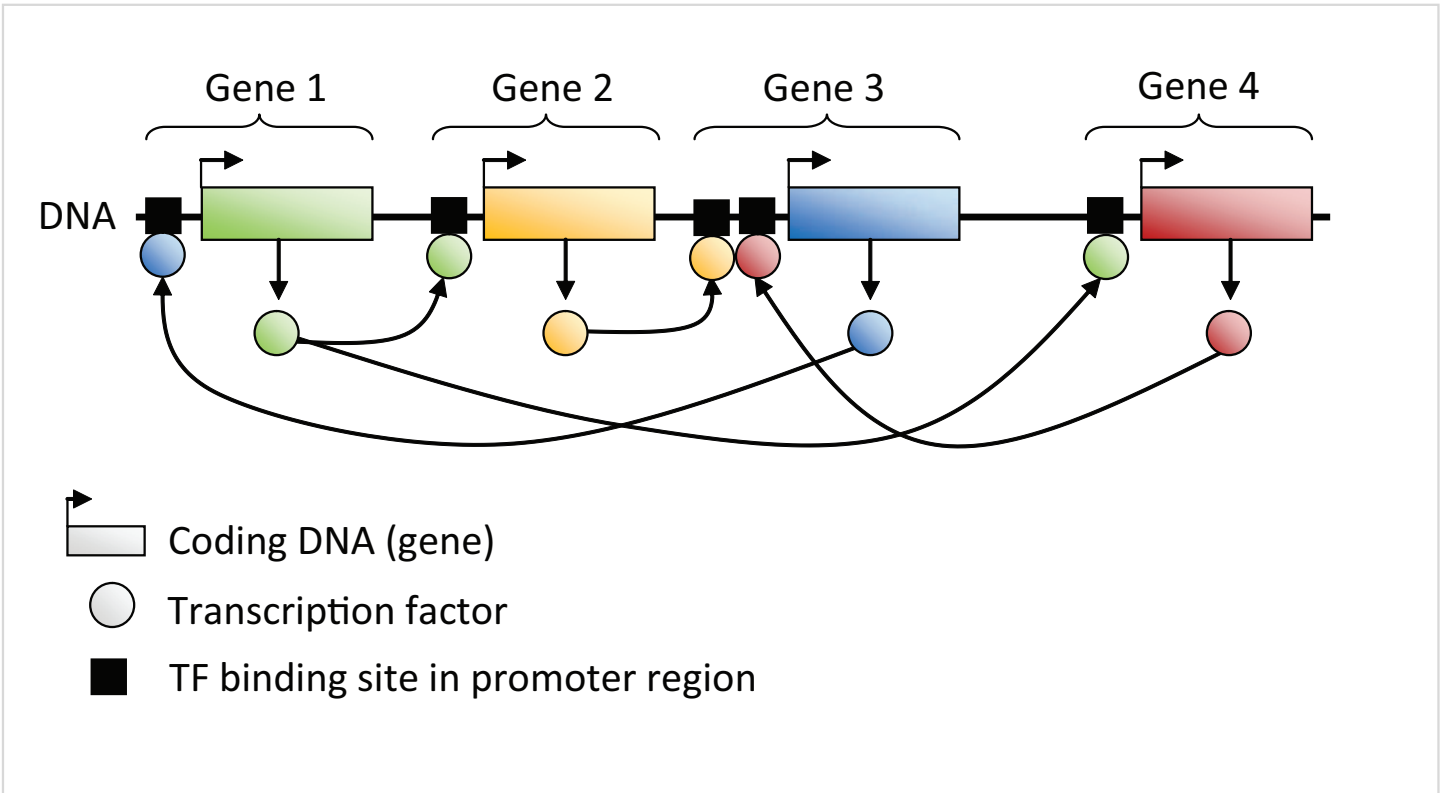

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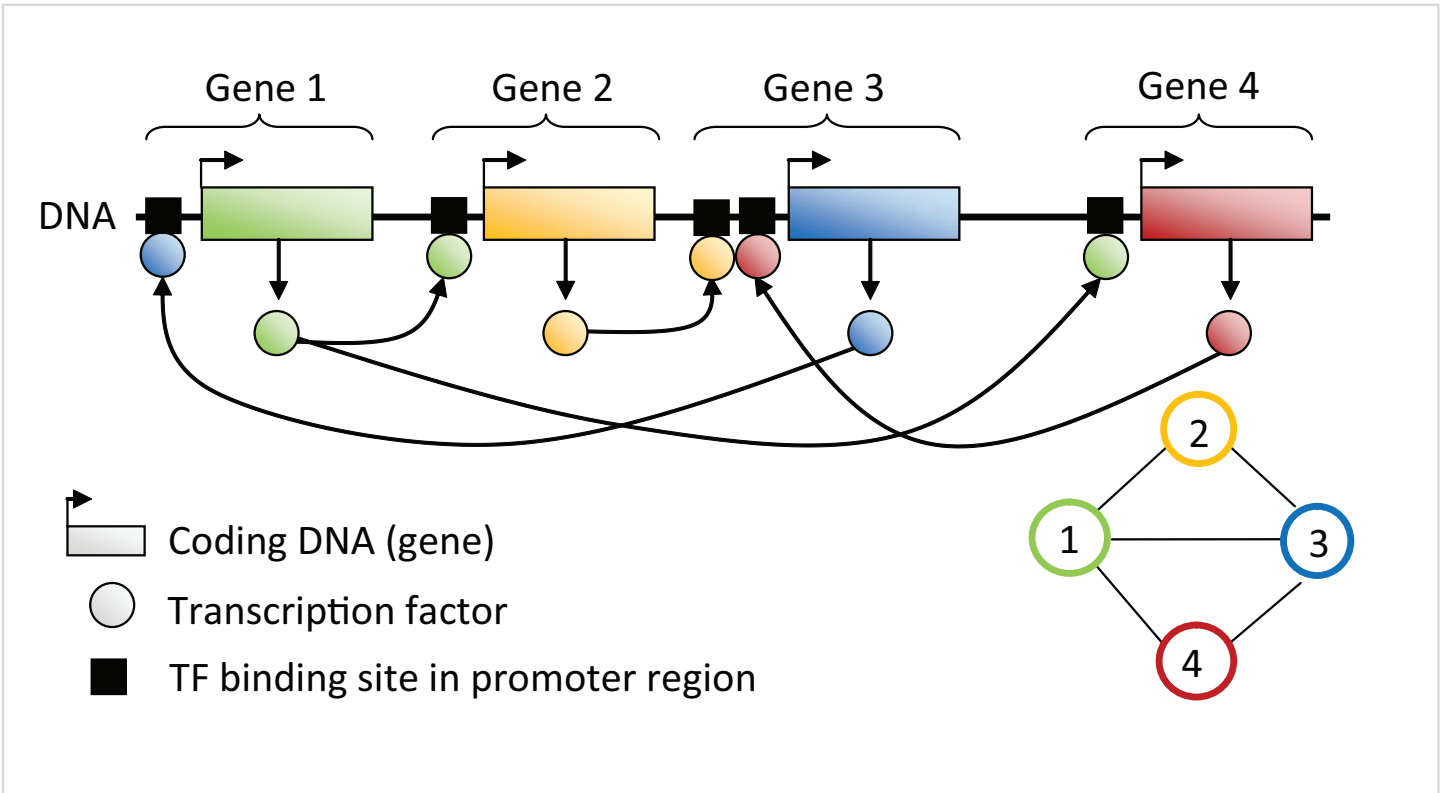

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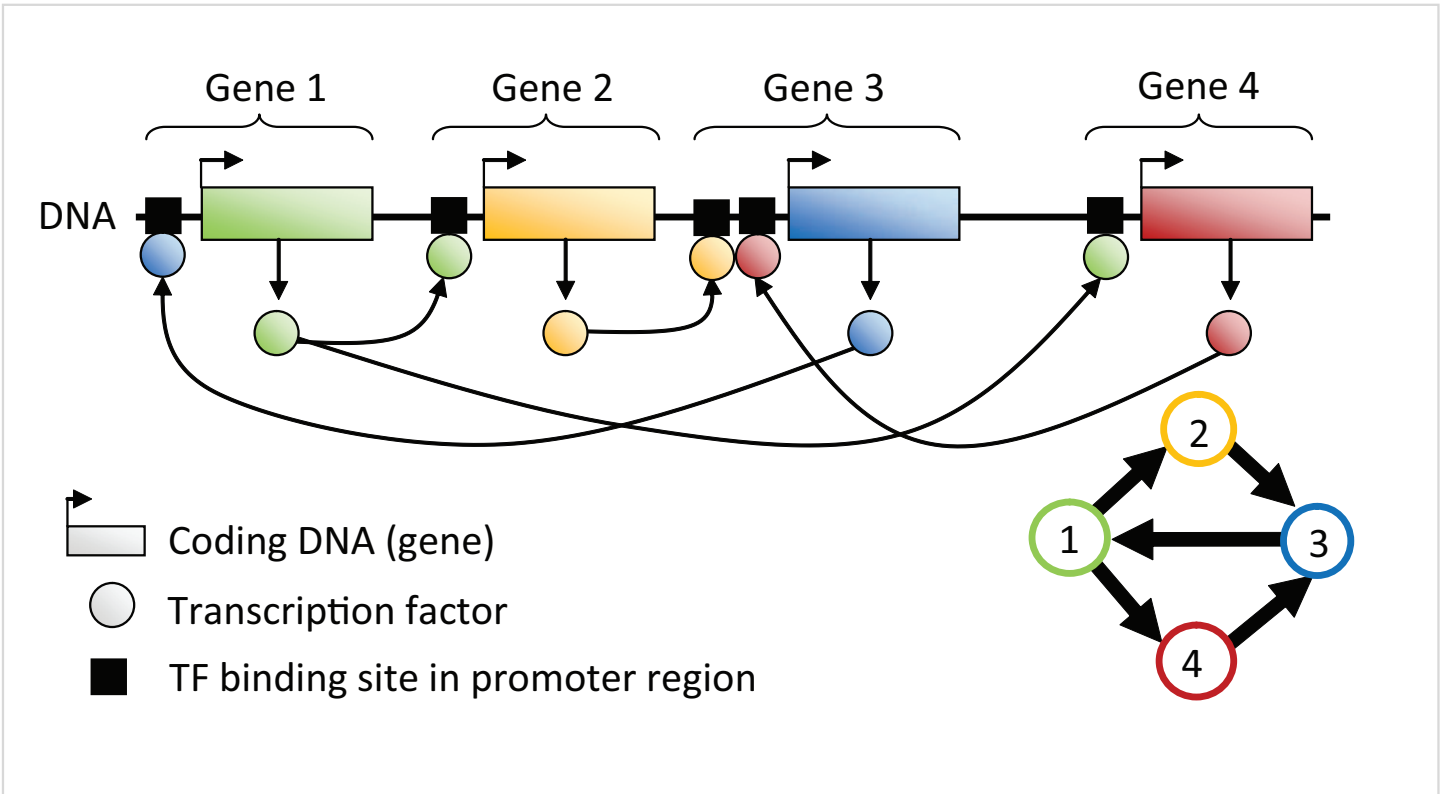

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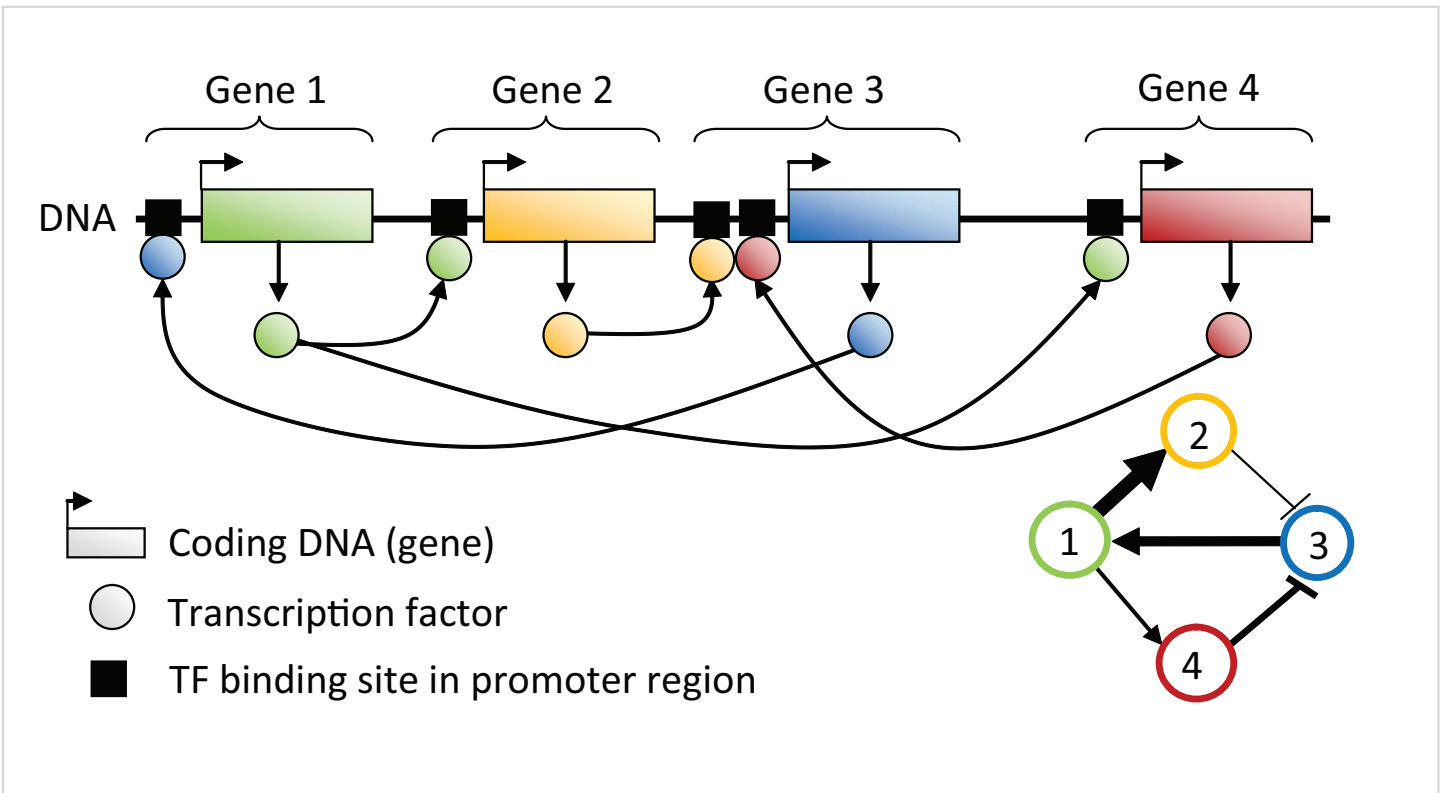

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Reverse Engineering Gene Regulatory Networks

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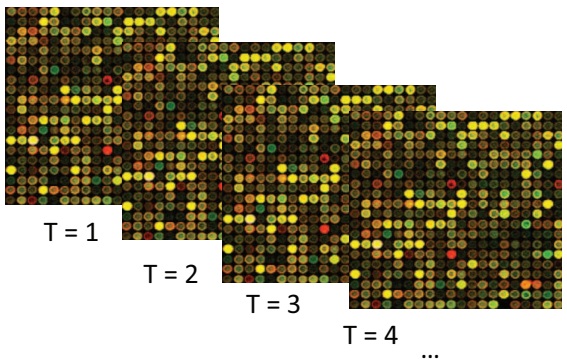

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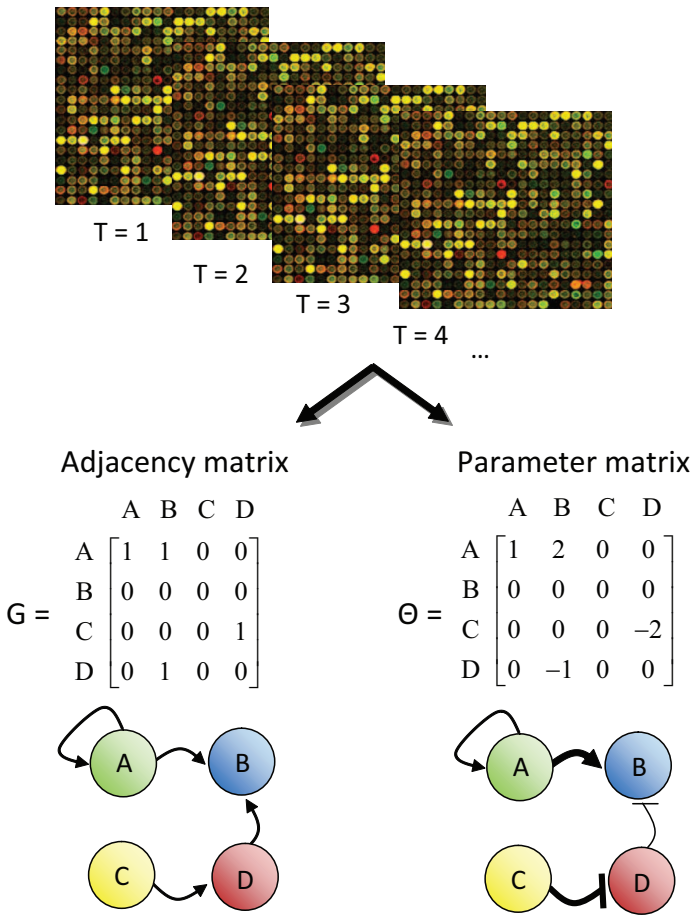

Bayesian Framework

- Let observed time-course gene expression data be $\mathbf{y} = \{\mathbf{y}_t : t = 1, \ldots, T\}$, where $\mathbf{y}_t = (y_{t1}, ..., y_{tP})^T$.

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- $\Rightarrow$ Fit model $f(\mathbf{y}|\theta)$ to observed data $\mathbf{y}$, where parameters are also random variables following $\pi(\theta)$.
  - Conditional distribution of network edges given observed data is $\pi(\theta|\mathbf{y}) \propto f(\mathbf{y}|\theta)\pi(\theta)$

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  - First applied in population genetics problems (e.g., Pritchard *et al.*, 1999; Beaumont *et al.*, 2002)
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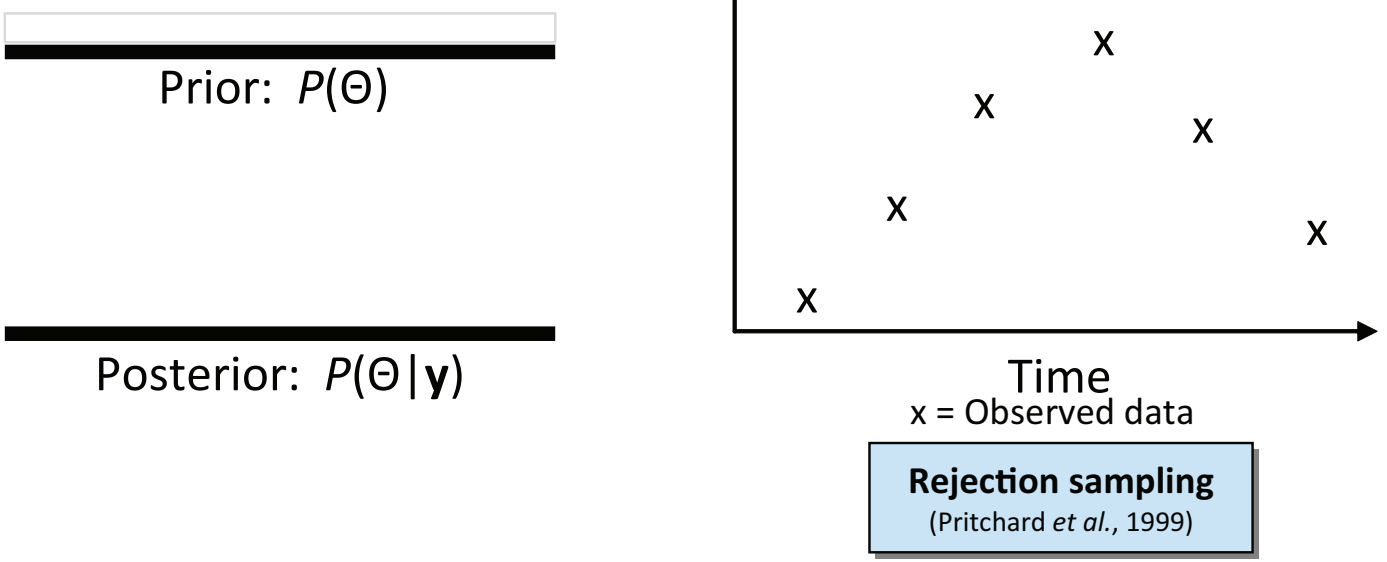
- Approximate when $\epsilon > 0$ and equivalent to simulating from the prior when $\epsilon \to \infty$

ABC Motivation



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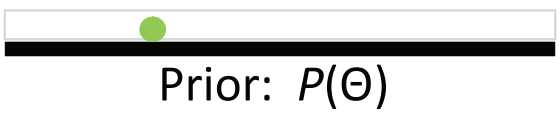

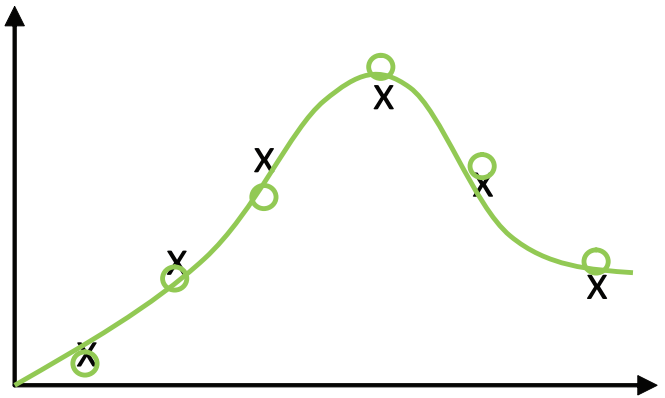

Rejection sampling
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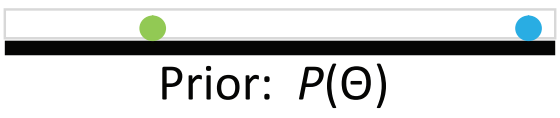

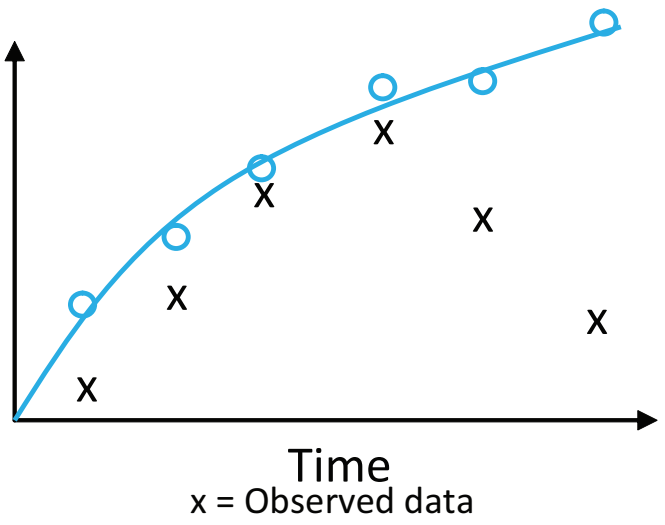

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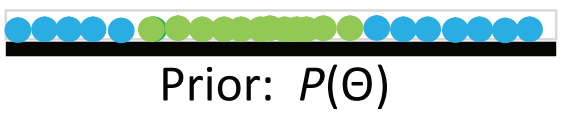
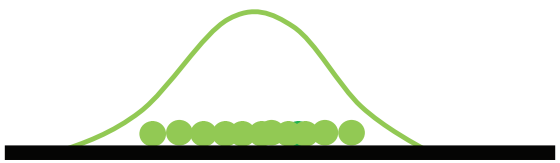
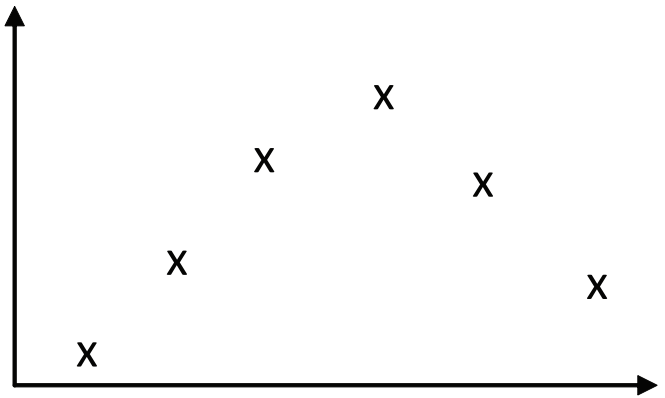


Prior: $P(\Theta)$



Posterior: $P(\Theta|\mathbf{y})$



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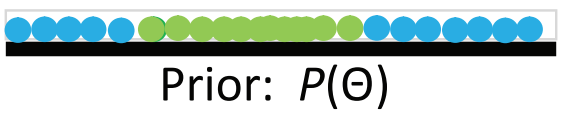

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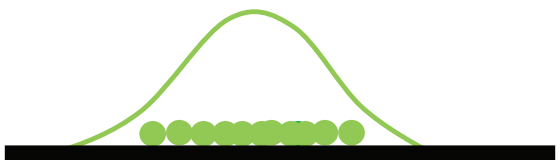
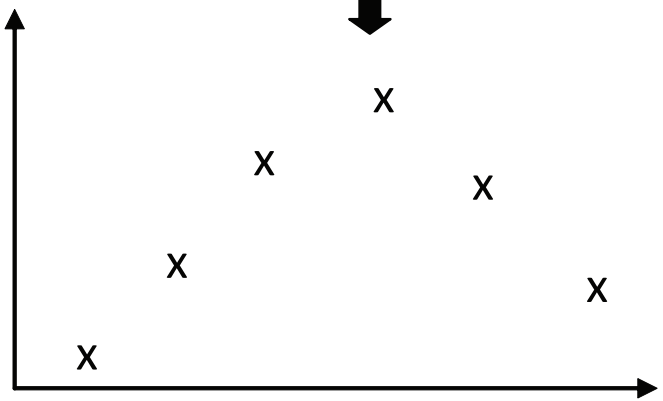


Posterior: $P(\Theta|\mathbf{y})$

- Tolerance/distance criteria
- Summary statistics
  (Beaumont *et al.*, 2002)



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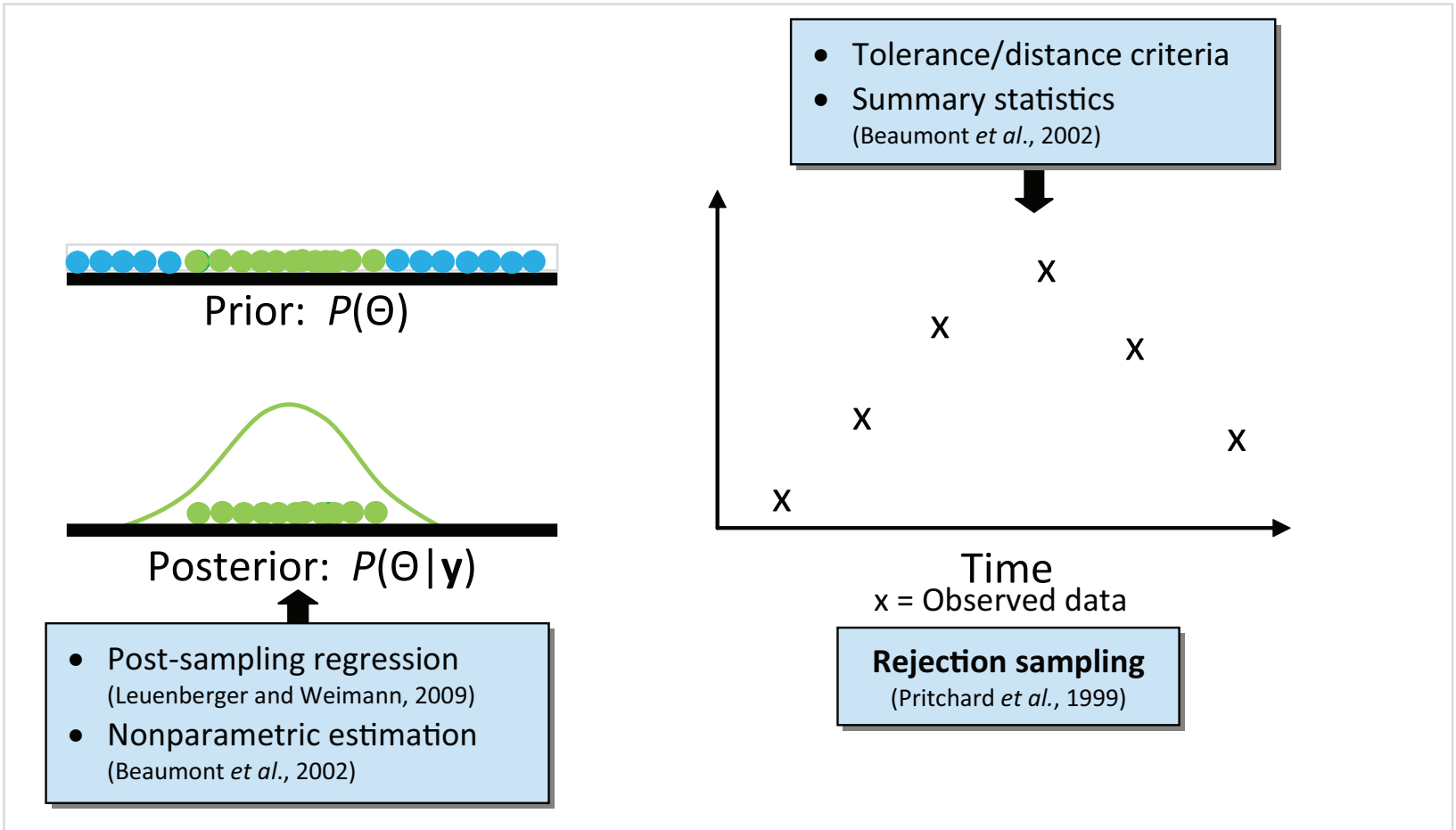

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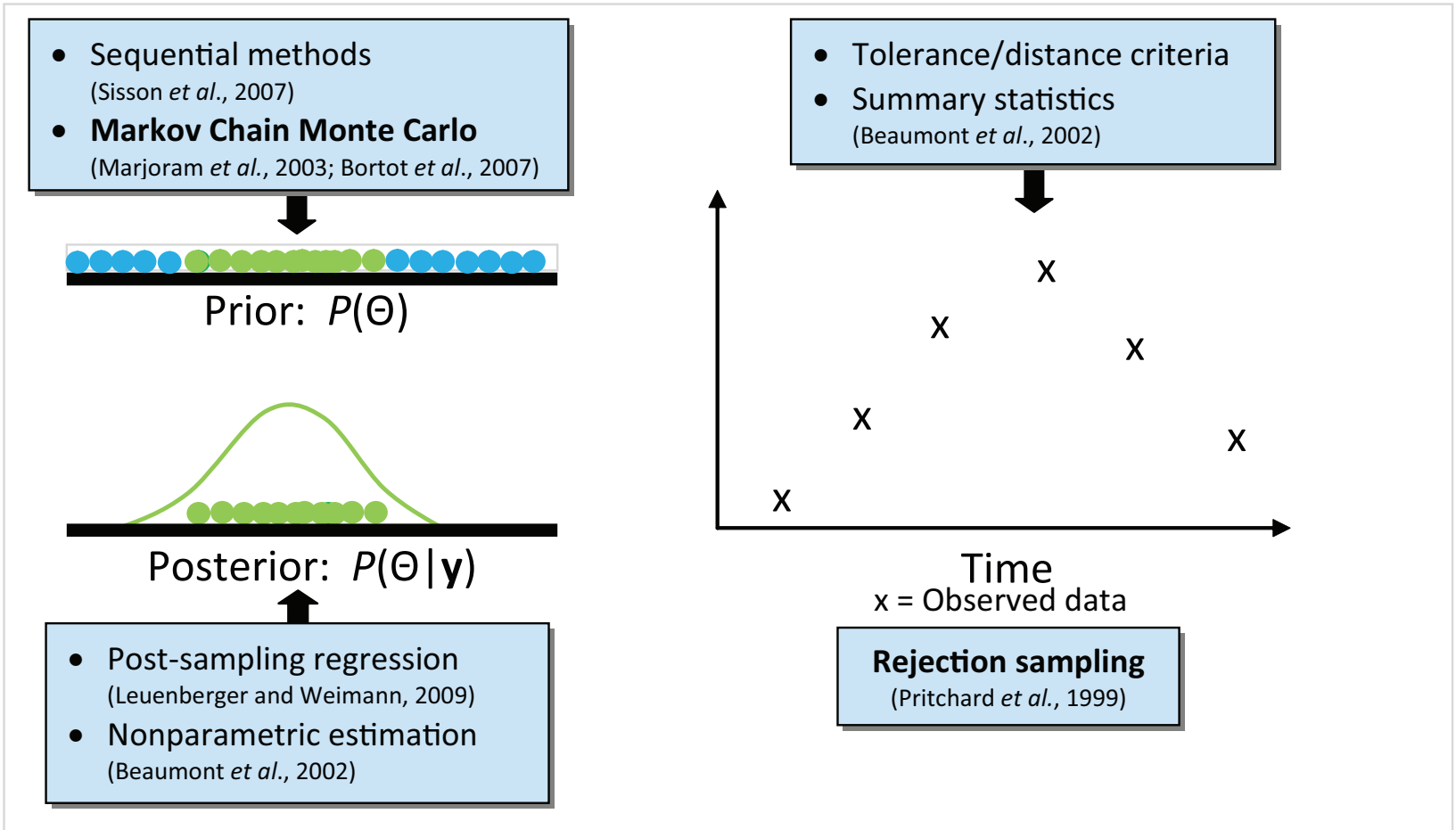

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ABC-MCMC (Marjoram et al., 2003)

- ABC-Markov chain Monte Carlo (MCMC): Construct a Markov chain (e.g., using Metropolis-Hastings algorithm) with approximate posterior distribution $\pi(\Theta|\rho(\mathbf{y}^\star, \mathbf{y}) \leq \epsilon)$ as equilibrium distribution (Marjoram et al., 2003) ▸ Details

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- Let $q(\cdot|\cdot)$ and $\pi(\cdot)$ be the transition and prior distributions, respectively.
- Given previous Θ^i, a proposed $\Theta^\star$ is accepted at the iterations with $(i+1)^{\text{st}}$ probability

$$\alpha = \min\left\{1, \frac{\pi(\Theta^\star)q(\Theta^i|\Theta^\star)}{\pi(\Theta^i)q(\Theta^\star|\Theta^i)}\mathbf{1}(\rho(\mathbf{y}^\star, \mathbf{y}) < \epsilon)\right\}$$

Adapting ABC-MCMC to Networks

- Several adaptations must be made to the ABC-MCMC method of Marjoram et al. (2003) for reverse engineering gene regulatory networks:

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  2. Appropriate distance function ρ and tolerance ϵ to compare simulated ($\mathbf{y}^\star$) and observed ($\mathbf{y}$) data
  3. Prior and proposal distributions for network structures

Simulating $\mathbf{y}^\star$ for Network $\Theta^\star$ (continuous)

Generally, we simulate gene expression at time t as a function of the gene expression at the previous time point:

$$\mathbf{y}_t^\star = f_t(\mathbf{y}_{t-1}, \Theta^\star)$$

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In practice, for continuous data (e.g., microarrays):

- Set $\mathbf{y}_1^\star = \mathbf{y}_1$.
- Generate one-step-ahead predictors based on first-order VAR model on gene expression for $t = 2, \ldots, T$:

$$\mathbf{y}_t^\star = \Theta^\star \mathbf{y}_{t-1}$$

▸ Details

Simulating $\mathbf{y}^\star$ for Network $\Theta^\star$ (discrete)

For count data (e.g., serial analysis of gene expression, RNA sequencing):

- Set $\mathbf{y}_1^\star = \mathbf{y}_1$.
- $\mathbf{y}_t \sim \text{Poisson}(\boldsymbol{\lambda}_t)$, where $\boldsymbol{\lambda}_t = \boldsymbol{\pi}_t y_{\cdot t}$, $\sum_{i=1}^{P} \pi_{it} = 1$, and $y_{\cdot t} = \sum_{i=1}^{P} y_{it}$.

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- Generate one-step-ahead predictors based on first-order VAR model on the *level* of gene expression for $t = 2, \ldots, T$:

$$\tilde{\boldsymbol{\pi}}_t^\star = \exp\left\{\frac{1}{y_{\cdot t-1}}\Theta^\star \mathbf{y}_{t-1}\right\} \text{ and } \boldsymbol{\pi}_t^\star = \frac{1}{\sum_{i=1}^P \tilde{\pi}_{it}^\star}\tilde{\boldsymbol{\pi}}_t^\star$$

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Distance Function and Tolerance

Distance functions (ρ):

- Canberra: $\rho(\mathbf{y}^\star, \mathbf{y}) = \sum_{t=1}^{T} \sum_{i=1}^{P} \frac{|y_{it}^\star - y_{it}|}{|y_{it}^\star + y_{it}|}$
- Euclidean: $\rho(\mathbf{y}^\star, \mathbf{y}) = \sqrt{\sum_{t=1}^{T} \sum_{i=1}^{P} (y_{it}^\star - y_{it})^2}$
- Manhattan: $\rho(\mathbf{y}^\star, \mathbf{y}) = \sum_{t=1}^{T} \sum_{i=1}^{P} |y_{it}^\star - y_{it}|$
- Multivariate Time Series (MVT):

$$\rho(\mathbf{y}^\star, \mathbf{y}) = \frac{1}{T} \sum_{t=1}^{T} [(\mathbf{y}_t - \mathbf{y}_t^\star) - (\hat{\mathbf{y}}_t - \hat{\mathbf{y}}_t^\star)]' \, \hat{\Sigma}^{-1} \, [(\mathbf{y}_t - \mathbf{y}_t^\star) - (\hat{\mathbf{y}}_t - \hat{\mathbf{y}}_t^\star)]$$

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Tolerance (ϵ):

- $\epsilon = 1\%$ quantile of distances ρ from 5000 random networks

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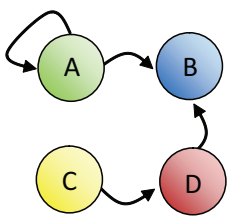
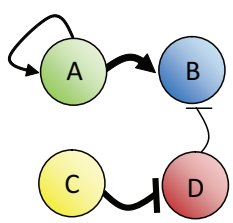
- To facilitate simulation, we introduce as an auxiliary variable a $P \times P$ adjacency matrix G, where $G_{ij} = 1$ if gene j regulates gene i, and $G_{ij} = 0$ otherwise.
- Note that $G_{ij} = 0 \Leftrightarrow \Theta_{ij} = 0$ and $G_{ij} = 1 \Leftrightarrow \Theta_{ij} \neq 0$

$$G = \begin{array}{c} \\ A \\ B \\ C \\ D \end{array} \begin{array}{c} \begin{array}{cccc} A & B & C & D \end{array} \\ \begin{bmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 \end{bmatrix} \end{array} \qquad \Theta = \begin{array}{c} \\ A \\ B \\ C \\ D \end{array} \begin{array}{c} \begin{array}{cccc} A & B & C & D \end{array} \\ \begin{bmatrix} 1 & 2 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -2 \\ 0 & -1 & 0 & 0 \end{bmatrix} \end{array}$$





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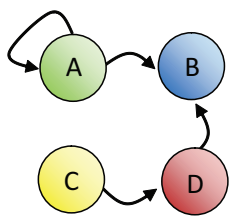
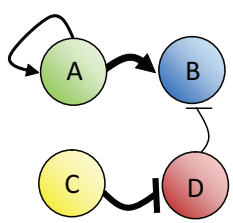




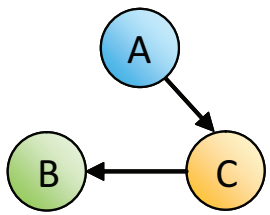
- Joint distribution of G and Θ may be seen as a completion to the marginal density of Θ

Two-Step Proposal Distribution

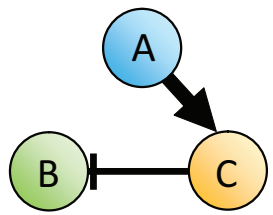
- Two-step proposal distribution: $q(G^\star|G^i)$ and $q(\Theta^\star|\Theta^i, G^\star)$:

Adjacency matrix

$$G^i = \begin{array}{c} \\ A \\ B \\ C \end{array} \begin{array}{c} \begin{array}{ccc} A & B & C \end{array} \\ \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 1 \\ 1 & 0 & 0 \end{pmatrix} \end{array}$$



Parameter matrix



$$\Theta^i = \begin{array}{c} \\ A \\ B \\ C \end{array} \begin{array}{c} \begin{array}{ccc} A & B & C \end{array} \\ \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & -2 \\ 3 & 0 & 0 \end{pmatrix} \end{array}$$

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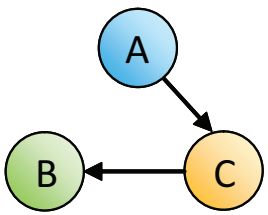

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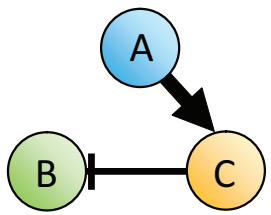

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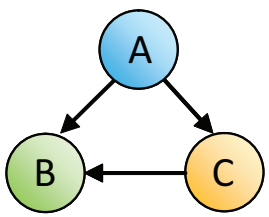
Add, delete, reverse edge
(Husmeier, 2003)

$$G^* = \begin{array}{c} \\ A \\ B \\ C \end{array} \begin{array}{c} \begin{array}{ccc} A & B & C \end{array} \\ \begin{pmatrix} 0 & 0 & 0 \\ 1 & 0 & 1 \\ 1 & 0 & 0 \end{pmatrix} \end{array}$$



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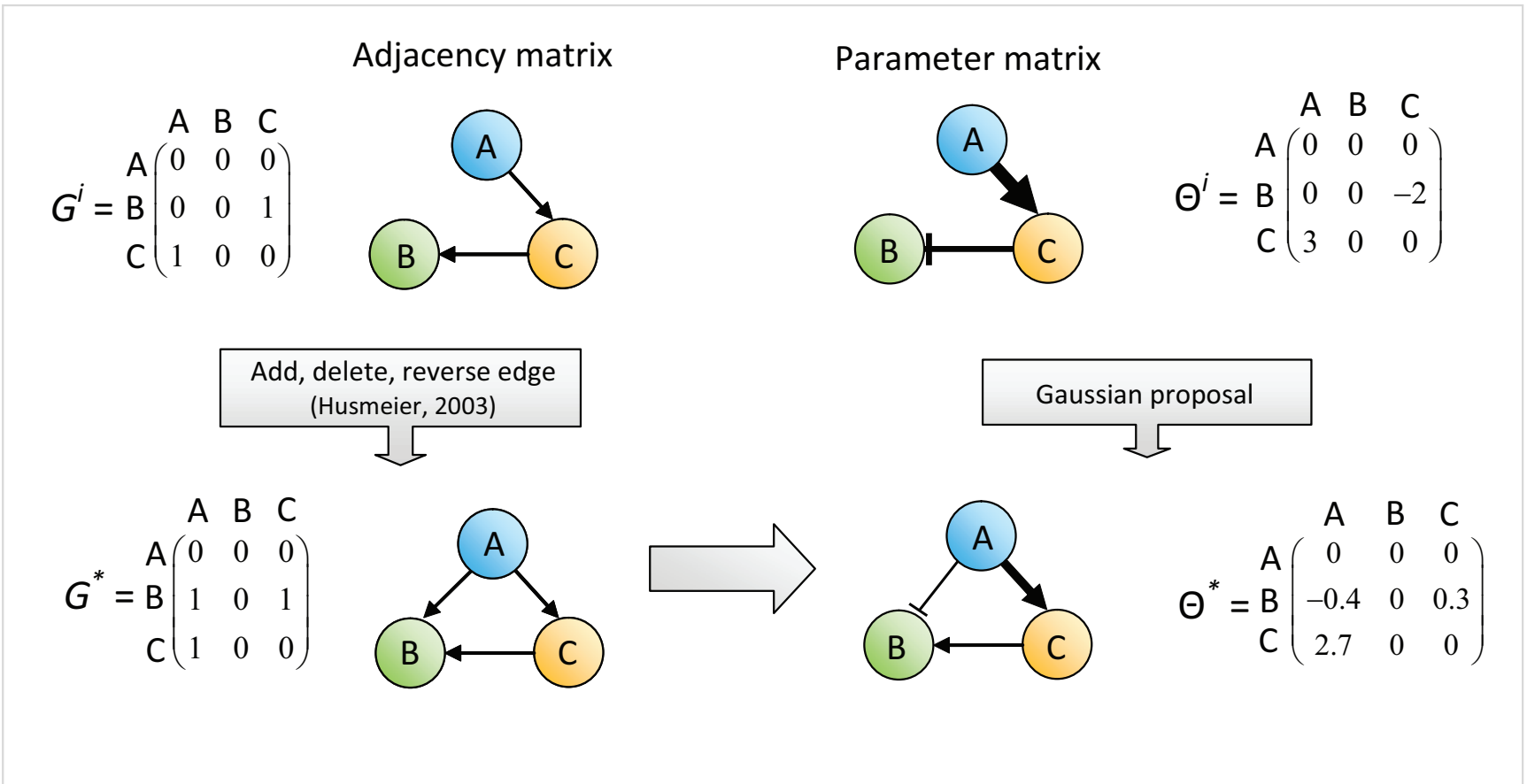
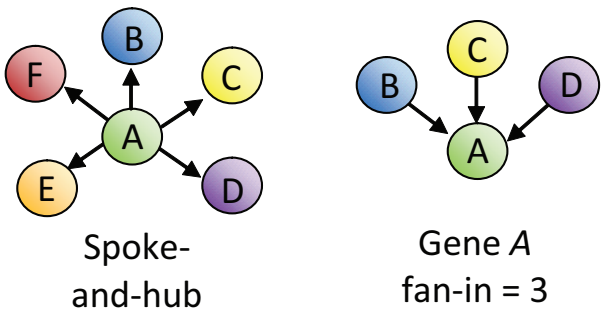


Prior Distributions

- Gene regulatory networks typically sparse with spoke-and-hub structure and few regulators per gene (fan-in)



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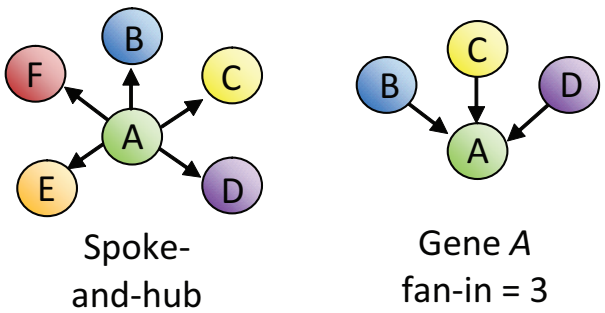

Prior distributions:

- $\pi(G)$ is uniform over all structures, with maximum fan-in of 5 or less
- $\pi(\Theta|G)$ is uniform

ABC-MCMC Network Method

ABC-Net Algorithm:

0. Initialize Θ^i, G^i, $i = 0$.

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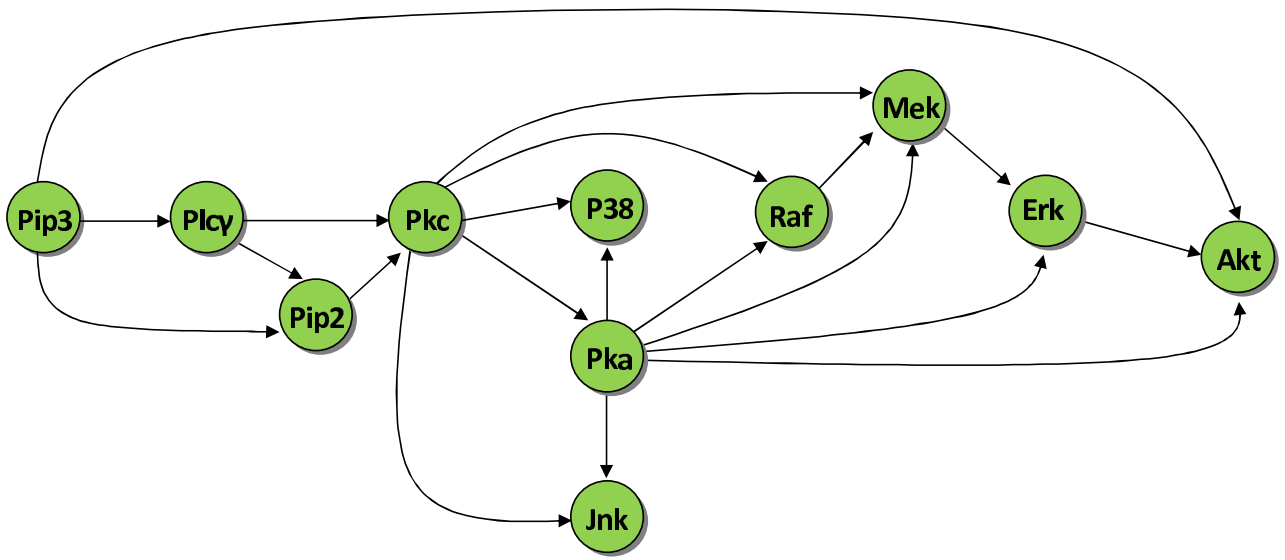
- Burn-in period, number of iterations, chain thinning, ... ▸ Details

Simulations: Raf Signalling Protein Pathway

- Simulations based on currently accepted gold-standard Raf signalling pathway (Sachs et al., 2005) in human immune system cells for 11 genes (20 total edges)



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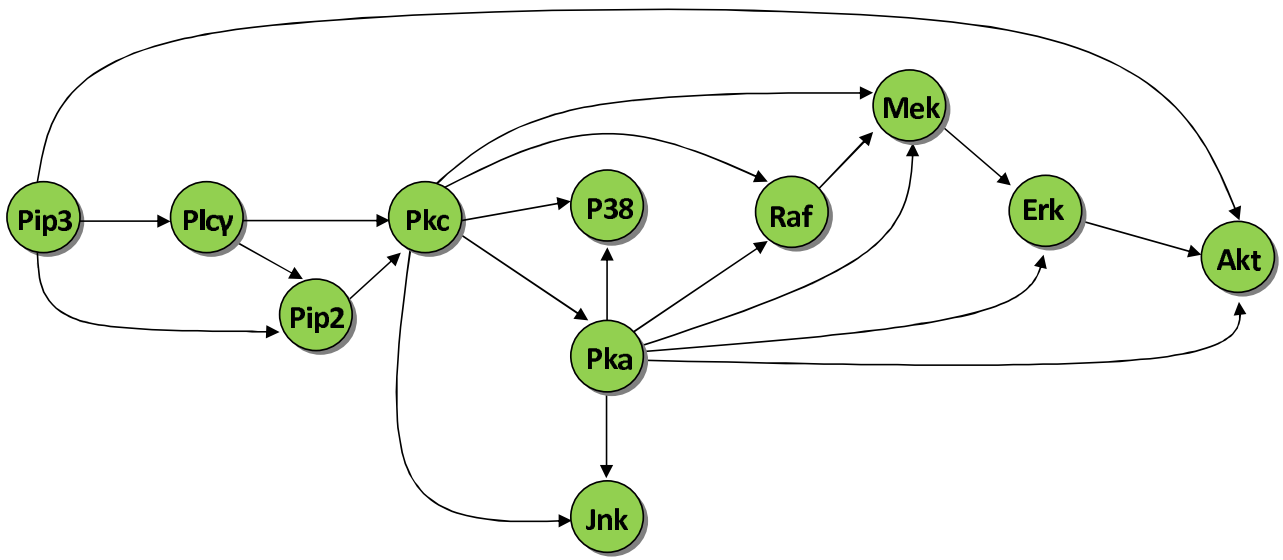


- Simulate $T = 20$ time points, $R = 1$ replicate using VAR model
- Run ABC-Net algorithm for 10 independent chains of length 1×10^6 with thinning interval of 50
- Use Gelman-Rubin statistic to assess convergence across chains

ABC-Net Simulations

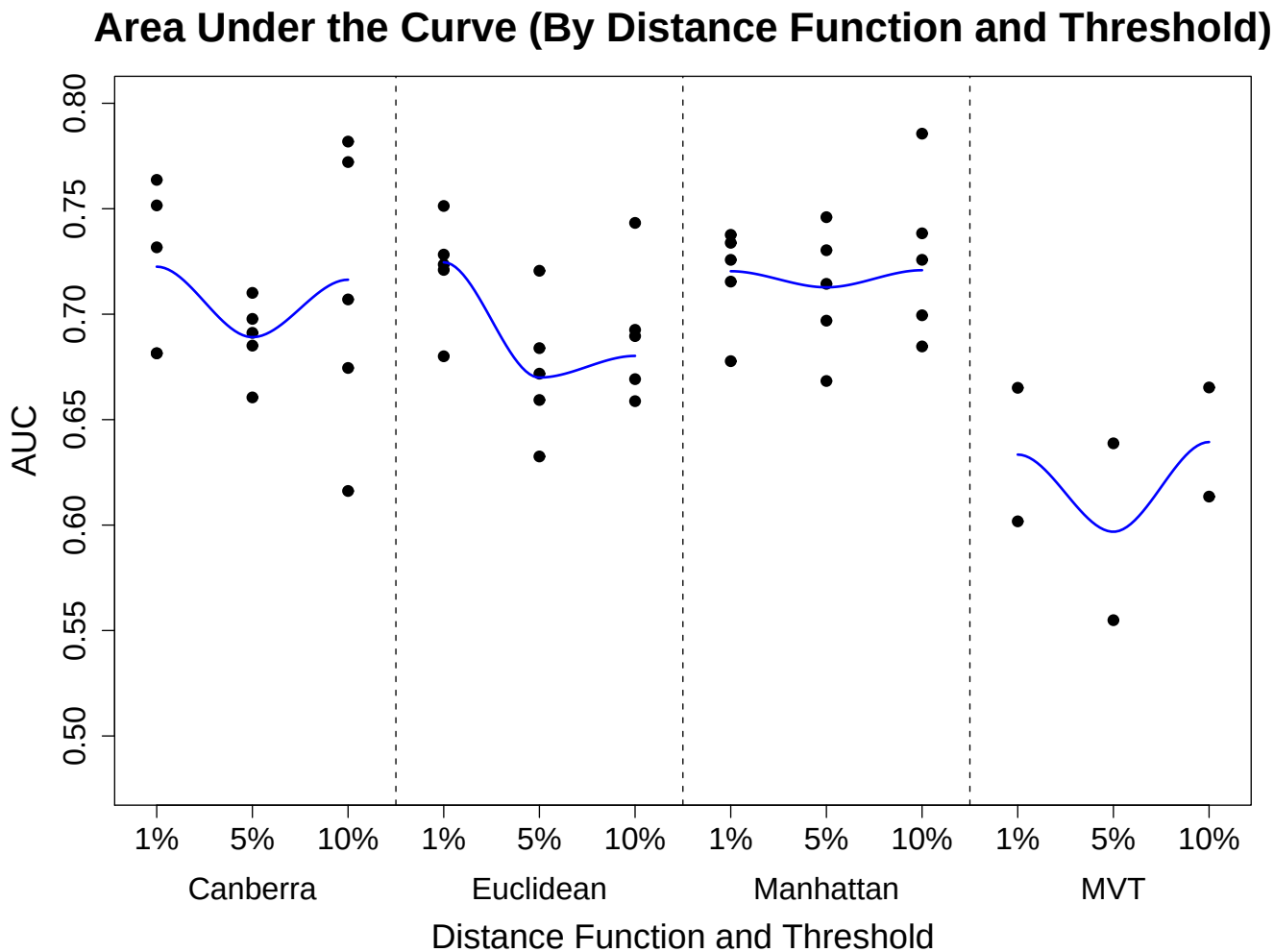
1. Choice of distance function ρ and tolerance ϵ

2. Suitability of VAR simulator for data generated with alternative models (nonlinear models, second-order models, and ordinary differential equations)

3. Sensitivity to prior distribution bounds

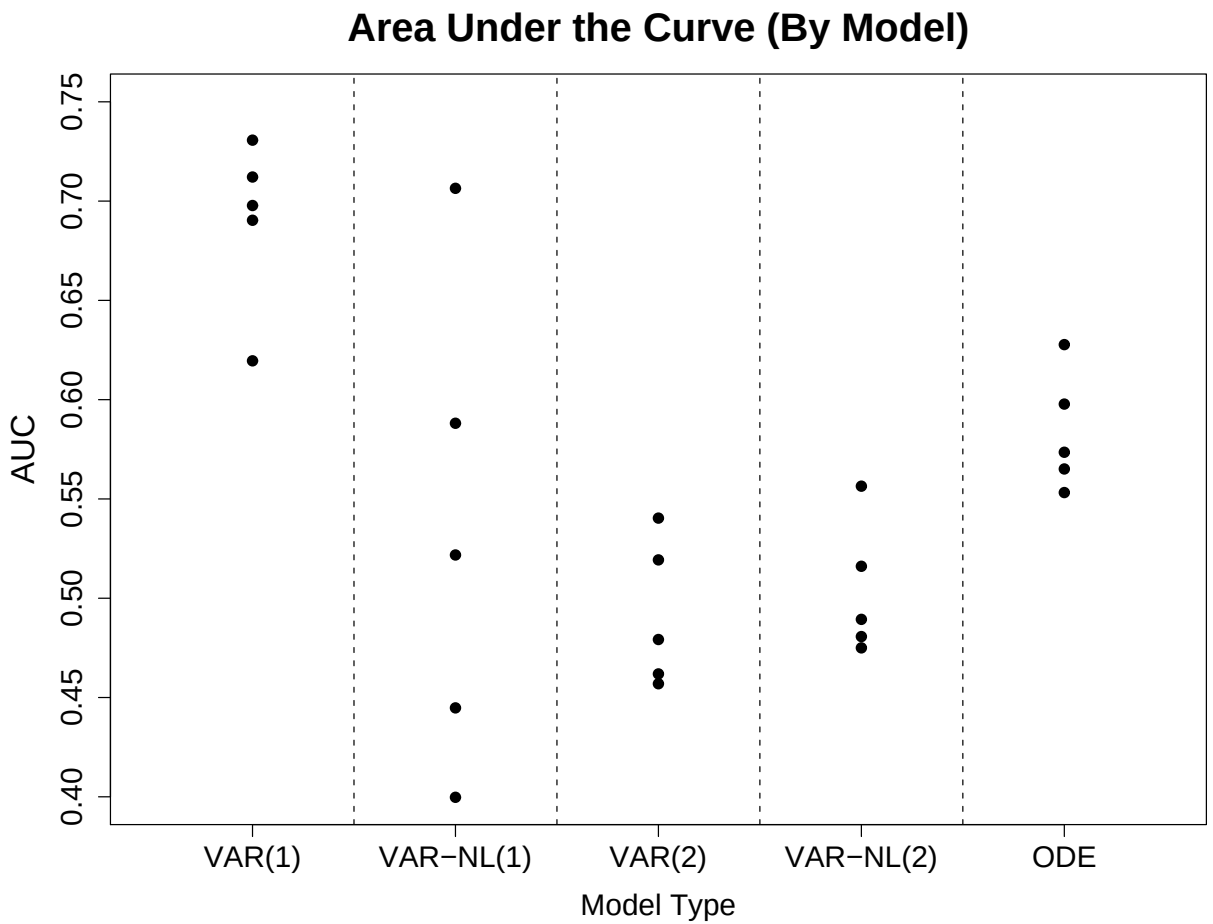
Simulations I: Choice of ρ and ϵ

- Set ϵ to be the 1%, 5%, or 10% quantile of distances ρ from 5000 random networks



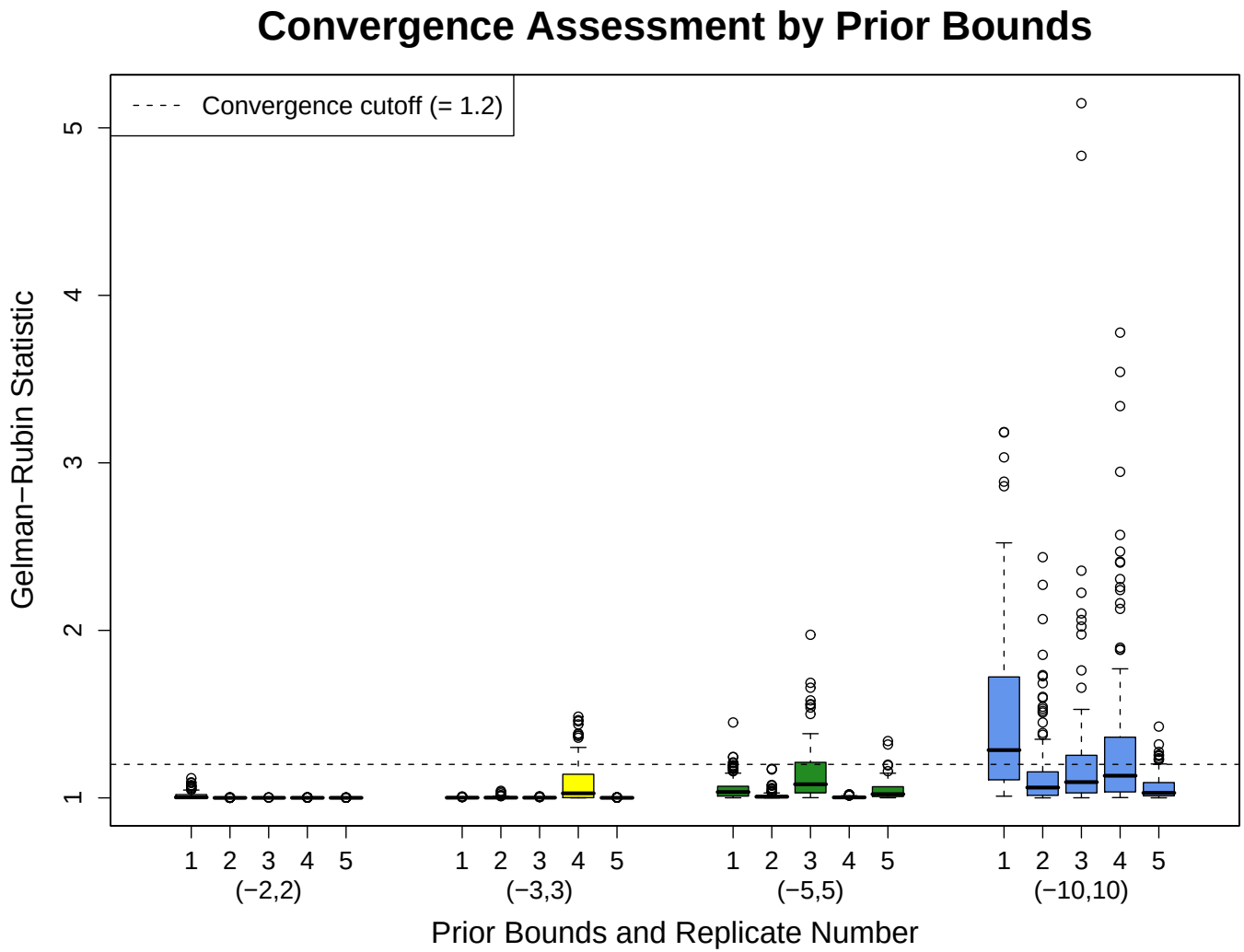
Simulations II: Suitability of VAR Simulator

- Alternative models: first-order nonlinear VAR (VAR-NL(1)), second-order VAR (VAR(2)), second-order nonlinear VAR (VAR-NL(2)), and ordinary differential equation (ODE)



Simulations III: Sensitivity to prior distribution bounds

- Vary prior bounds $\pi(\Theta|G)$ between (-2,2), (-3,3), (-5,5) and (-10,10)



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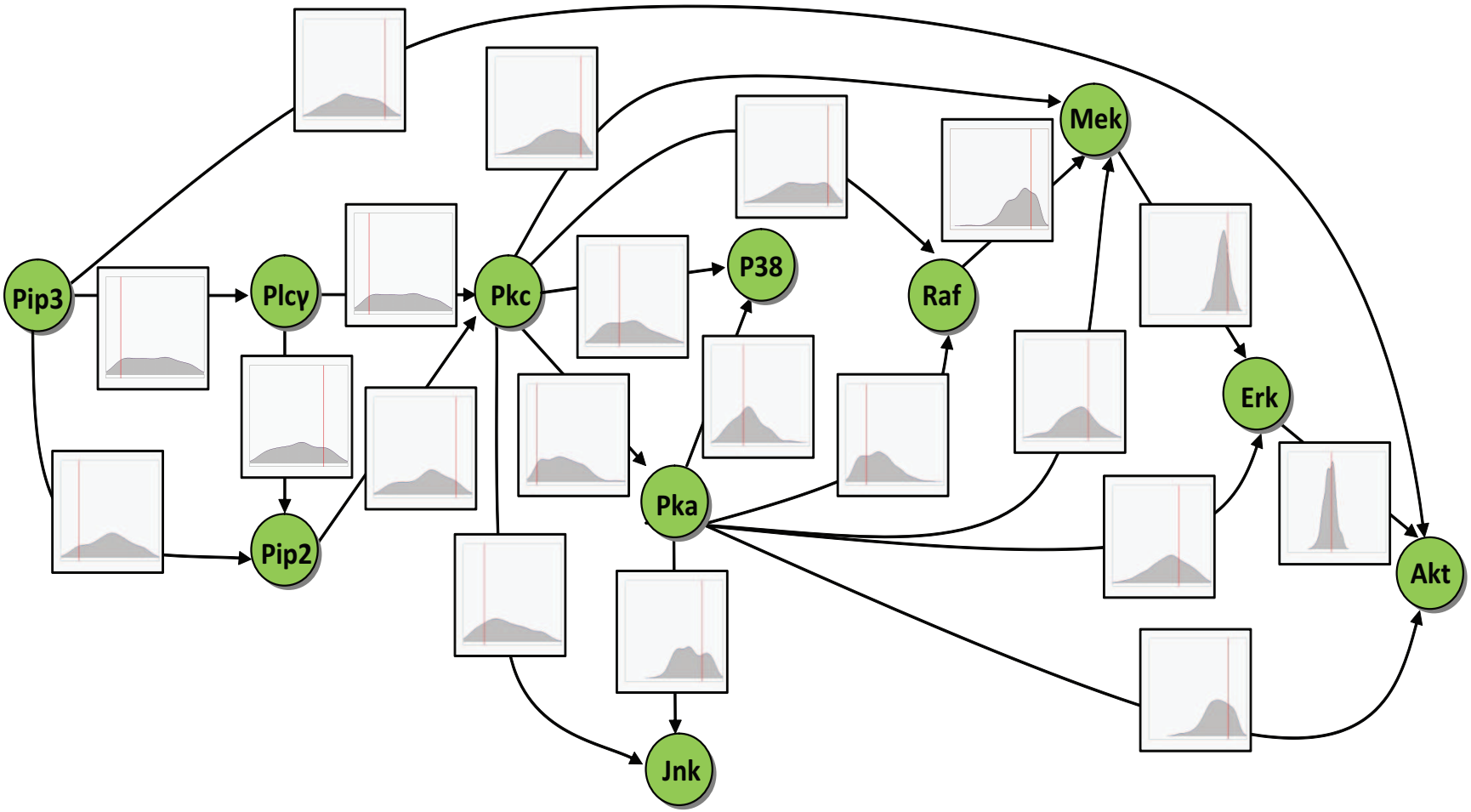

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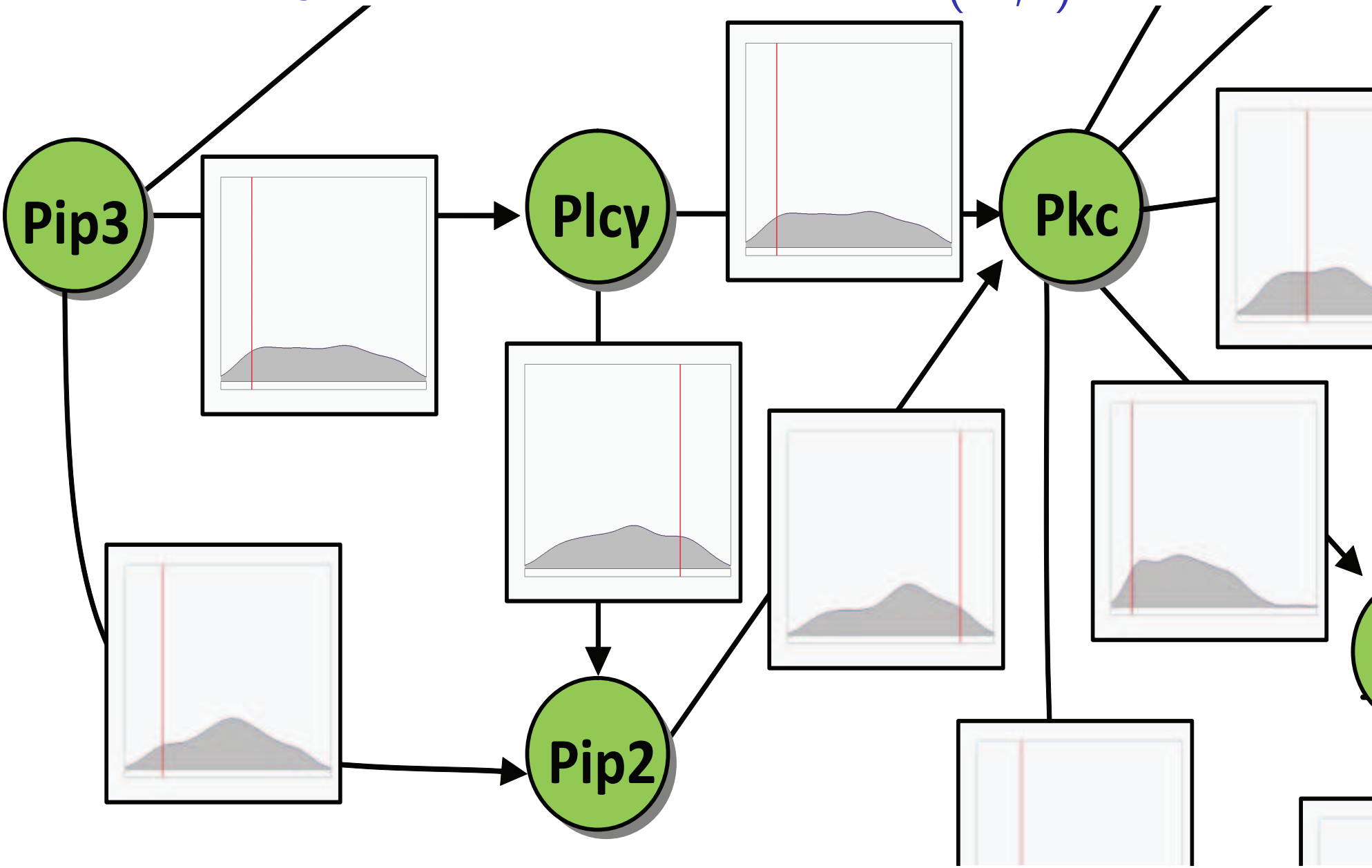

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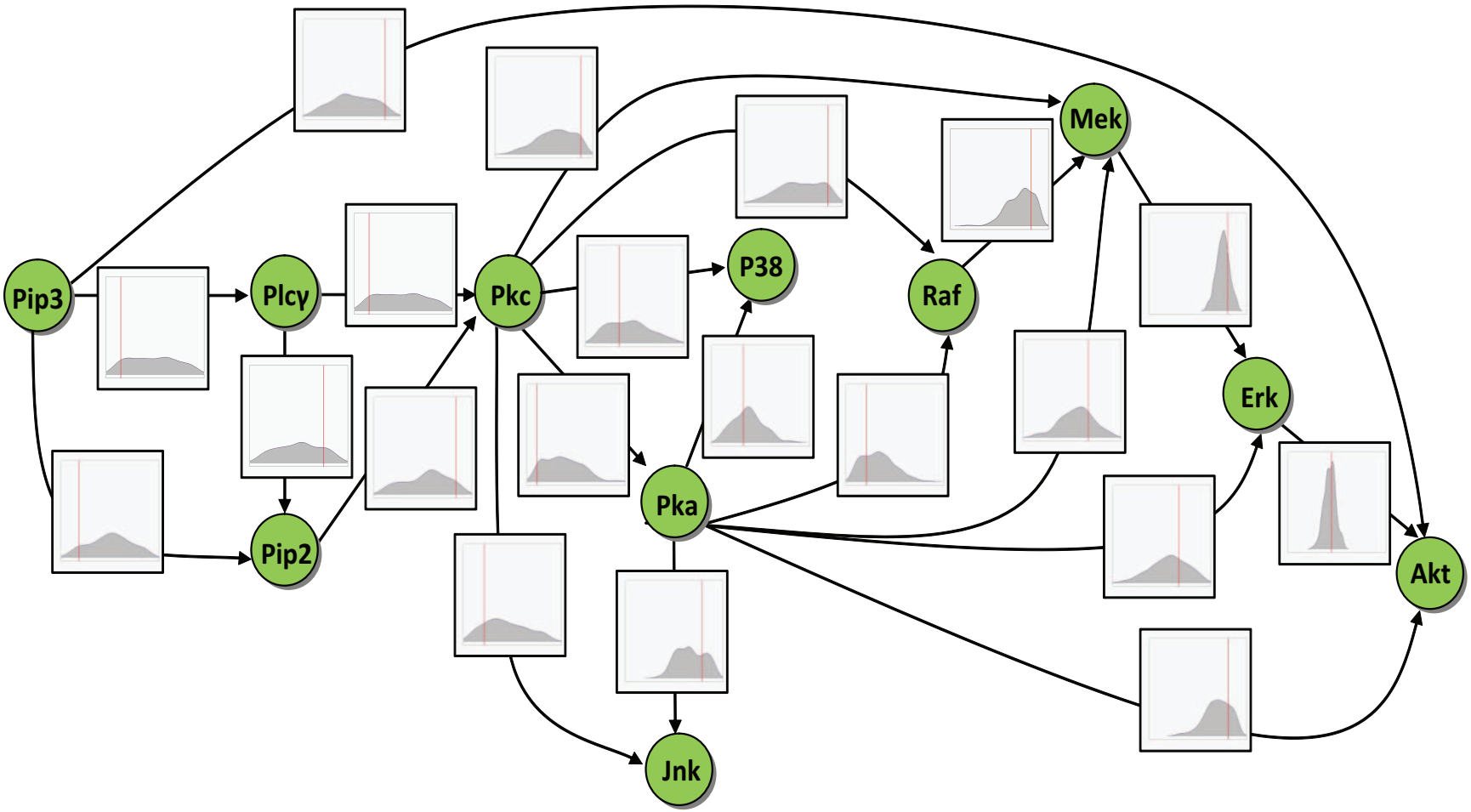

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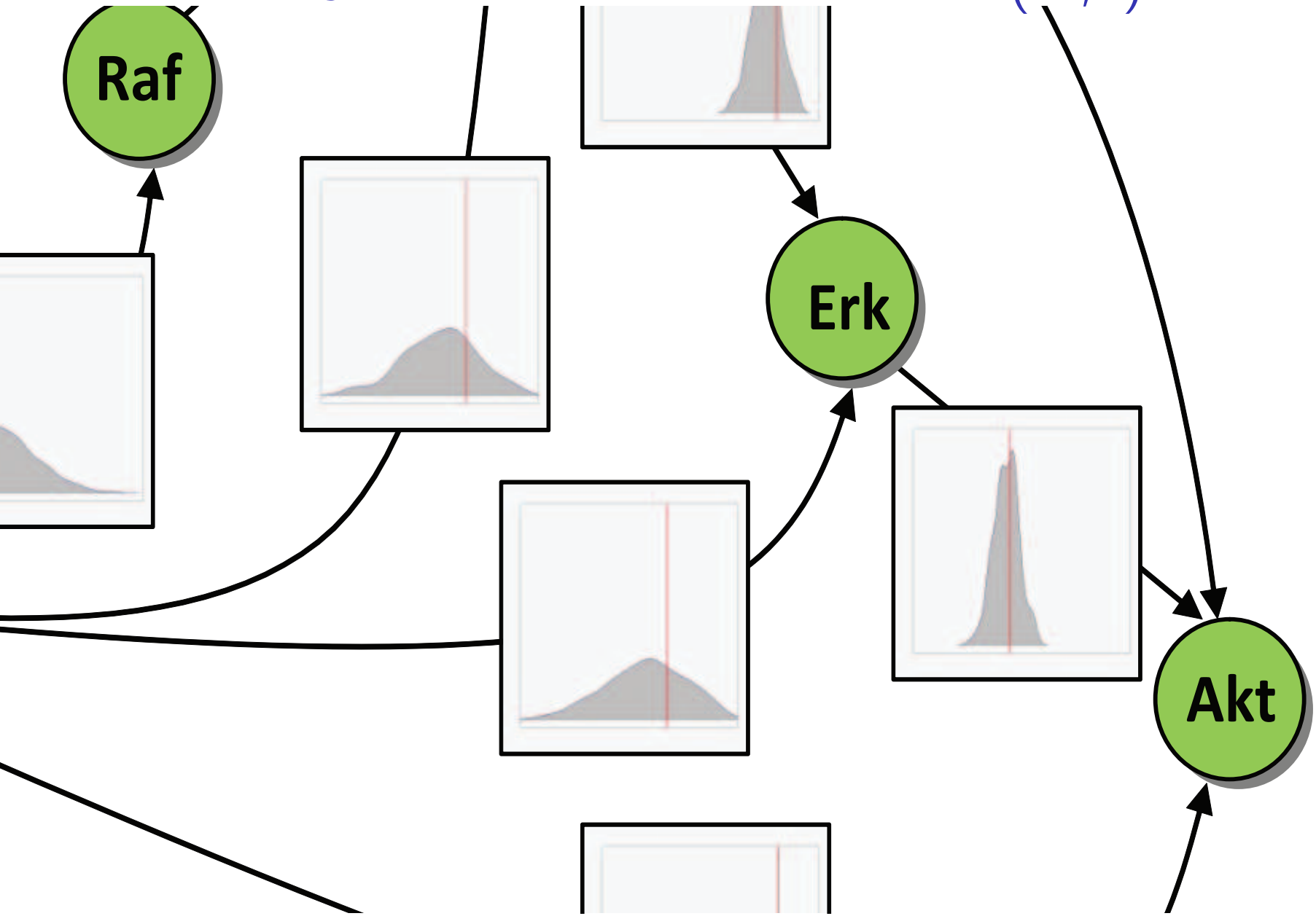

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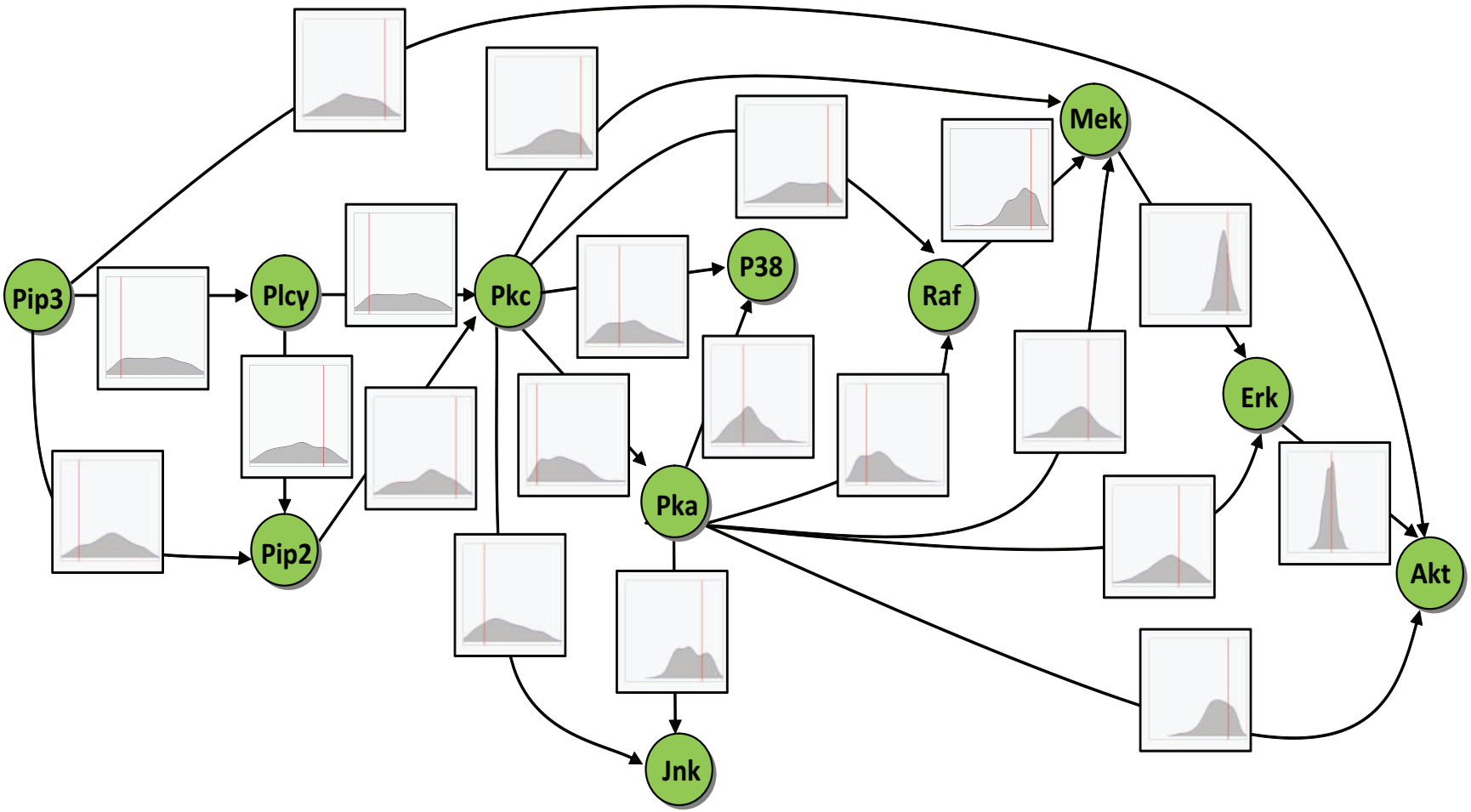

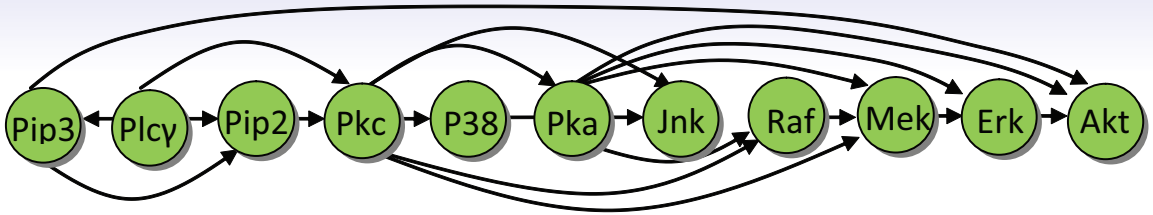
Pip3
Plcγ
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P38
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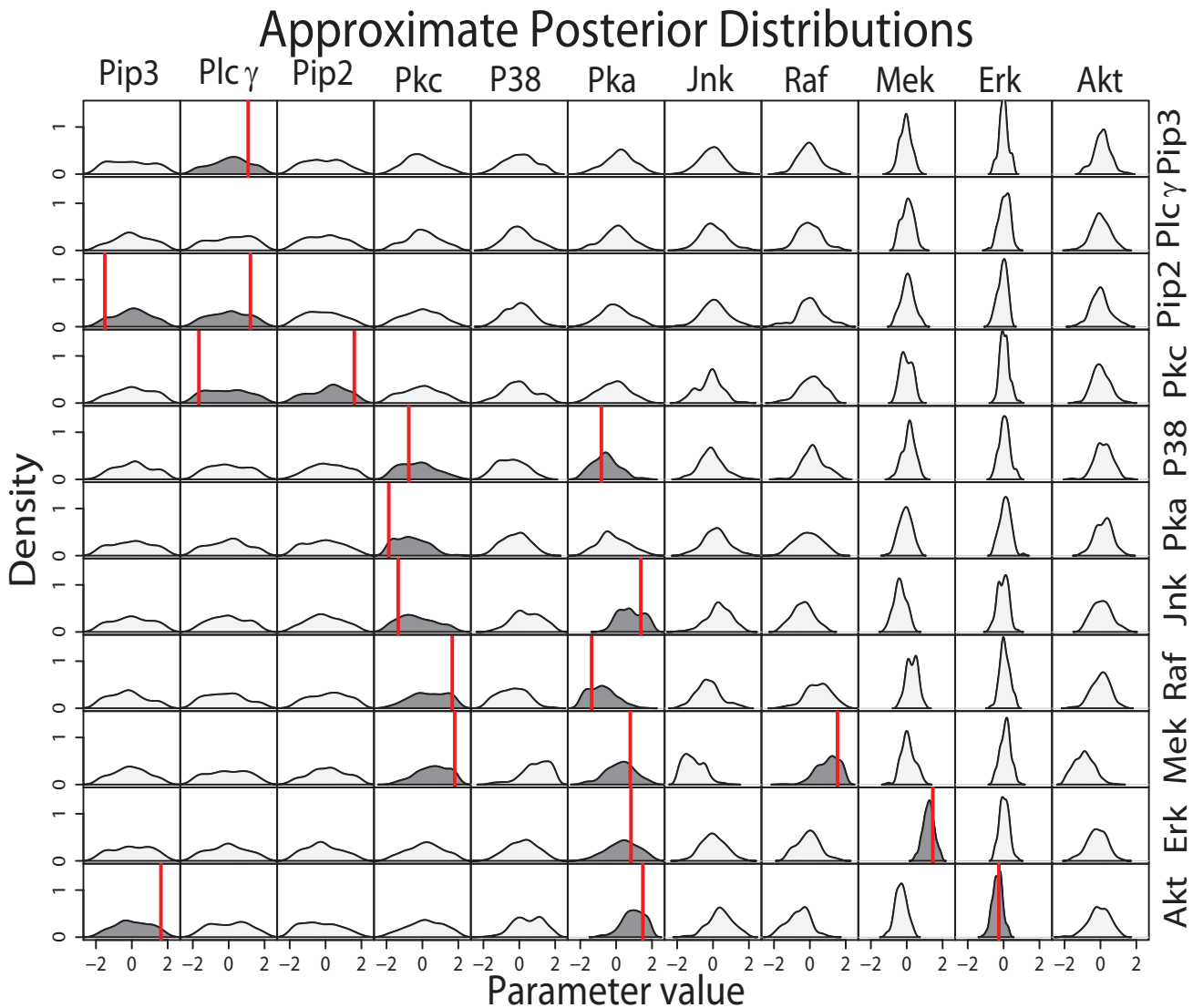
Approximate Posterior Distributions
Pip3
Plc γ
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Density
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- Wider prior bounds lead to convergence problems and may require more iterations

Data Analysis

- Different inference methods are better suited to different tasks:
  - Empirical Bayes Dynamic Bayesian Network (EBDBN) method (Rau et al. (2010)) is a hierarchical (empirical) Bayesian method for moderately sized networks (e.g., 50 - 100 genes):

$$\pi(\Theta|\mathbf{y}, \hat{\psi}) \propto f(\mathbf{y}|\Theta)\pi(\Theta|\hat{\psi})\pi(\hat{\psi})$$

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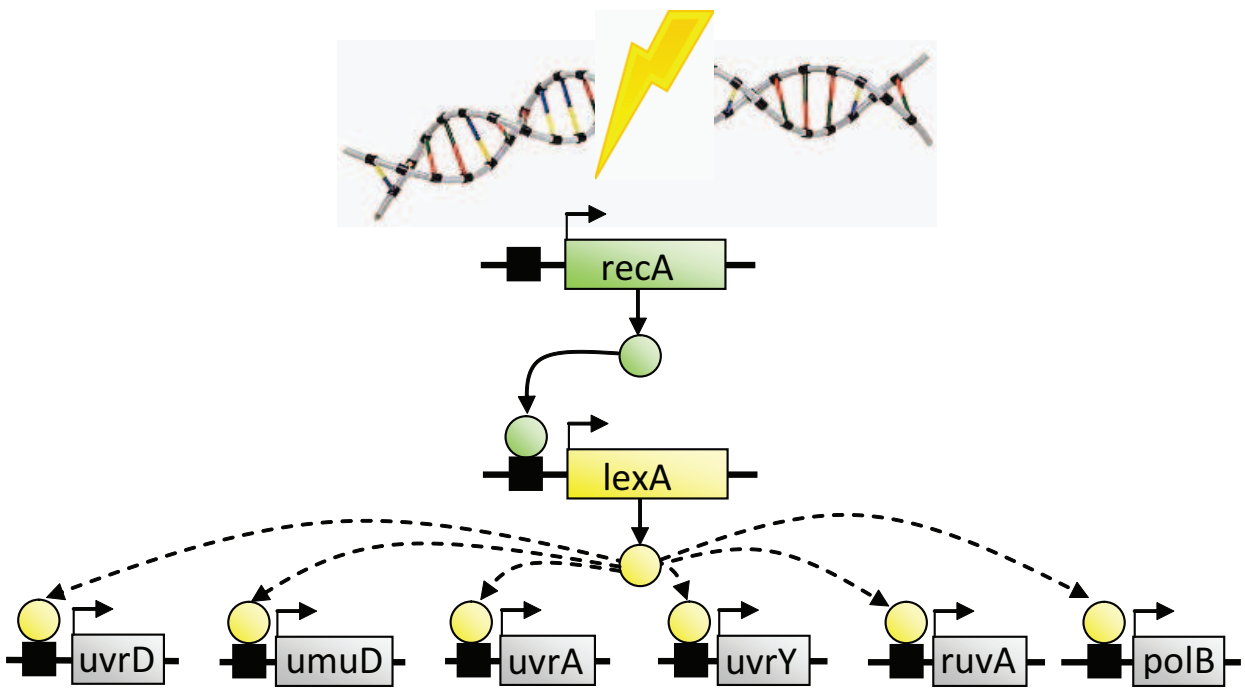
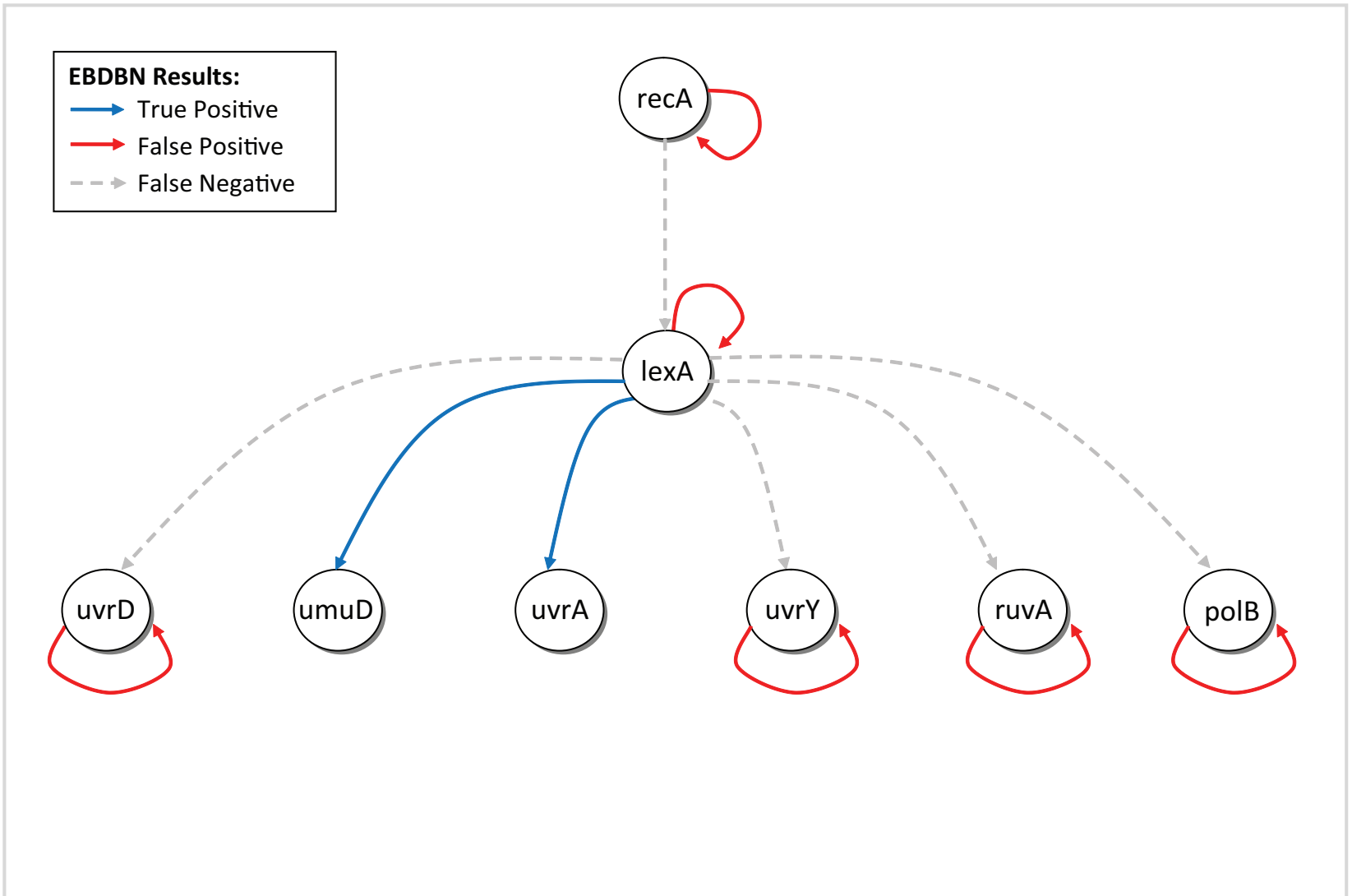
  - ABC-Net algorithm may be used for detailed analyses of small, well-characterized networks (e.g., 10 - 20 genes)
- Using two algorithms on a common task can help elucidate the strengths and weaknesses of each one:
  - S.O.S. DNA repair system in *Escherichia coli*

Data Analysis: S.O.S. DNA Repair System in *E. coli*

- S.O.S. DNA repair system of *Escherichia coli* (Ronen et al., 2002)
- 8 genes, with lexA as a master regulator that inhibits S.O.S. genes under normal conditions but activates them when DNA damage is sensed by recA ("single-input" module architecture)
- 50 time points, 1 replicate
- Maximum fan-in for ABC-Net method constrained to 2



Results: S.O.S. DNA Repair System



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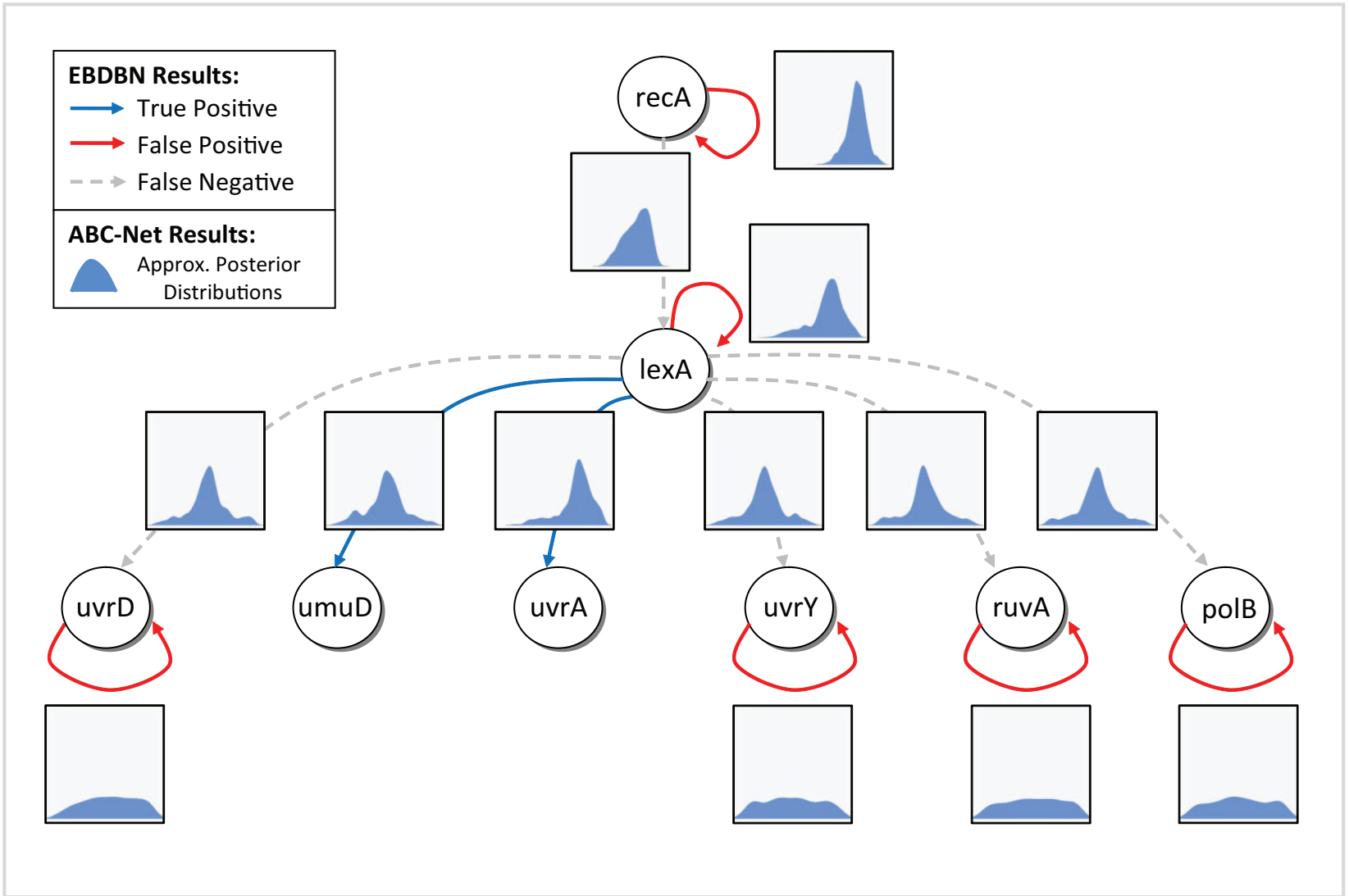

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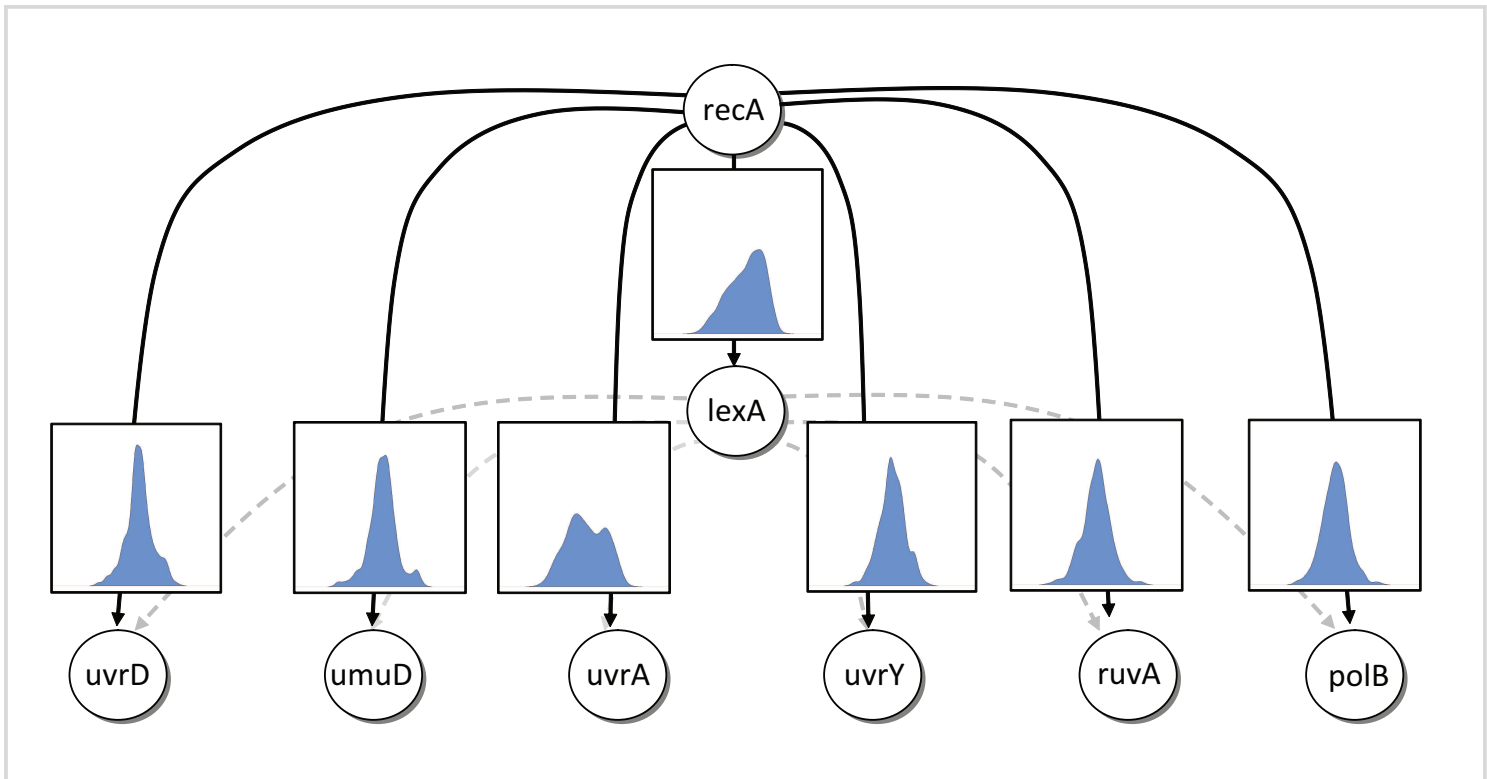

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- "Rigid" and "flexible" edges identified by the ABC-Net algorithm can help clarify results from other inference methods

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- Approximate Bayesian Computation methods can reveal information about the dynamics of biological systems from time-series gene expression data
- ABC-MCMC Network (ABC-Net) approach uses a simulation-based Bayesian method with few distributional assumptions to infer approximate posterior distributions in small networks

Future Work

- Further examine components of ABC-Net method:
  - More sophisticated data simulators and techniques to identify optimal simulators for real data
  - Alternative and efficient network structure proposal schemes
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- Develop statistical methods to combine results from multiple inference methods (i.e., consensus networks or model averaging)

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RWD research group
My Truong
Doug Crabill

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Likelihood-Free MCMC

Theorem

Under suitable regularity conditions, $\pi(\Theta|\rho(\mathbf{y}, \mathbf{y}^\star) \leq \epsilon)$ *is the stationary distribution of the chain.*

Likelihood-Free MCMC

Theorem

Under suitable regularity conditions, $\pi(\Theta|\rho(\mathbf{y}, \mathbf{y}^\star) \leq \epsilon)$ *is the stationary distribution of the chain.*

Let $r(\Theta \to \Theta^\star)$ be the transition mechanism of the chain. We must check whether $f(\Theta|\rho(\mathbf{y}^\star, \mathbf{y}) \leq \epsilon) r(\Theta \to \Theta^\star) = f(\Theta^\star|\rho(\mathbf{y}^\star, \mathbf{y}) \leq \epsilon) r(\Theta^\star \to \Theta)$.

Proof.

Without loss of generality, choose $\Theta^\star \neq \Theta$ such that

$$\frac{\pi(\Theta^\star)q(\Theta|\Theta^\star)}{\pi(\Theta)q(\Theta^\star|\Theta)} \leq 1$$

Detailed balance equation:

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$$= f(\Theta|\rho(\mathbf{y}^\star,\mathbf{y}) \leq \epsilon)q(\Theta^\star|\Theta)\mathbb{P}\left[\rho(\mathbf{y}^\star,\mathbf{y}) \leq \epsilon|\Theta^\star\right]\alpha(\Theta,\Theta^\star)$$

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$$\begin{aligned} f(\Theta|\rho(\mathbf{y}^\star,\mathbf{y}) \leq \epsilon) r(\Theta \to \Theta^\star) = \\ &= f(\Theta|\rho(\mathbf{y}^\star,\mathbf{y}) \leq \epsilon) q(\Theta^\star|\Theta) \mathbb{P}\left[\rho(\mathbf{y}^\star,\mathbf{y}) \leq \epsilon|\Theta^\star\right] \alpha(\Theta,\Theta^\star) \\ &= \frac{\mathbb{P}\left[\rho(\mathbf{y}^\star,\mathbf{y}) \leq \epsilon|\Theta\right]\pi(\Theta)}{\mathbb{P}\left[\rho(\mathbf{y}^\star,\mathbf{y}) \leq \epsilon\right]} \left\{ q(\Theta^\star|\Theta)\mathbb{P}\left[\rho(\mathbf{y}^\star,\mathbf{y}) \leq \epsilon|\Theta^\star\right] \times \frac{\pi(\Theta^\star)q(\Theta|\Theta^\star)}{\pi(\Theta)q(\Theta^\star|\Theta)} \right\} \end{aligned}$$

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Simulation Procedure

- One-step-ahead predictors: $\mathbf{y}^\star = \Theta^\star \mathbf{y}_{t-1}$
  - Suppose we have complete knowledge from the past ($\mathbf{y}_{t-1}$) and we want to predict (simulate) expression at time t based on the current network $\Theta^\star$: $\mathbf{y}_t^\star = \hat{\mathbf{y}}_t = E(\mathbf{y}_t | \mathbf{y}_{t-1}, \Theta^\star)$.
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- Marjoram *et al*. (2003): DNA sequences simulated using coalescent trees

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LFN Implementation Details

- Burn-in period
  - Cooling procedure: Temper acceptance with exponential cooling scheme, starting at some initial temperature ϵ_0 and cooling to $\epsilon_{i+1} = \lambda\epsilon_i$ until the minimal temperature $\epsilon_{\text{min}} = \epsilon$ is reached. We use $\lambda = 0.90$ and set $\epsilon_0 = \epsilon\lambda^{-10}$.
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- Chain length:
  - 10 chains for 1×10^6 iterations each (1×10^7 iterations total)
  - Thinning interval of 50 (2×10^5 remaining iterations)
  - Inference made on samples corresponding to smallest 1% of $\rho(\mathbf{y}^\star, \mathbf{y})$ (2000 iterations)

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Approximate Bayesian Methods I

Empirical Bayes Dynamic Bayesian Network (EBDBN) Algorithm

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- Idea: Use observed data $\mathbf{y}$ to estimate $\boldsymbol{\psi}$
- Common parametric EB models (based on conjugate distributions) include Poisson-Gamma, Beta-binomial, multinomial-Dirichlet, and **Gaussian-Gaussian**
- Let $\mathbf{y}_t$ and $\mathbf{x}_t$ be observed gene expression and unobserved hidden states measured at time t:

$$\mathbf{x}_t = \mathbf{A}\mathbf{x}_{t-1} + \mathbf{B}\mathbf{y}_{t-1} + \mathbf{w}_t$$
$$\mathbf{y}_t = \mathbf{C}\mathbf{x}_t + \mathbf{\Theta}\mathbf{y}_{t-1} + \mathbf{v}_t$$
$$\mathbf{w}_t \sim N(0, I), \mathbf{v}_t \sim N(0, V^{-1}))$$

Empirical Bayes Dynamic Bayesian Network (EBDBN): Rau *et al.*, 2010

Let $\mathbf{y} = \{\mathbf{y}_t\}_{t=1,\ldots,T}$ be observed gene expression and $\mathbf{x} = \{\mathbf{x}_t\}_{t=1,\ldots,T}$ be unobserved hidden states measured at the same time points.

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- Linear Gaussian state space model:

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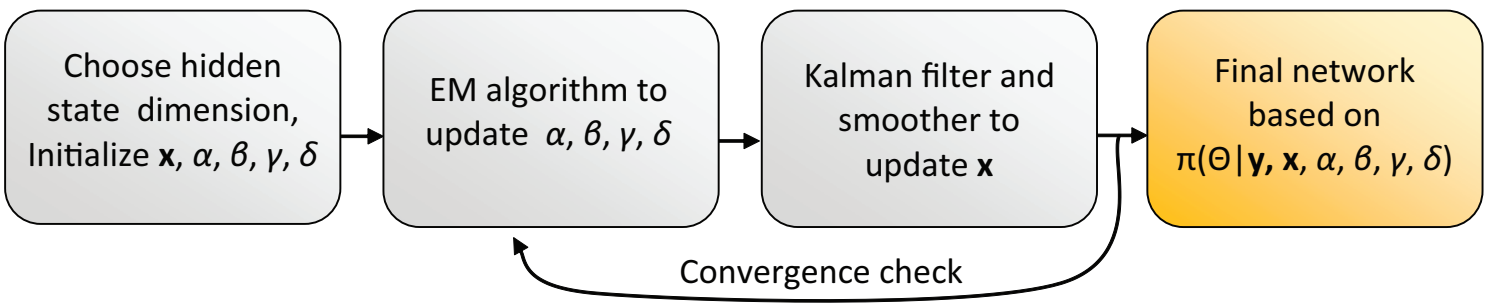

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